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Formation of C-C Bonds via Transfer Hydrogenation: From Methodology Development to Natural Product Synthesis

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Formation of C-C Bonds via Transfer Hydrogenation: From Methodology Development to Natural Product Synthesis

by

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Dedication

To My Parents – Aimin & Ping

and My Wife – Fang

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And my wife, Fang Fan, she is always understading and supporting me; I cannot imagine any single day in my life without her. Last but not least, I would like to thank my parents, Aimin Ge and Ping Gao, for their endless love, encouragement and patience to me. It would be impossible for me to be where I am right now without their full support.

Formation of C-C Bonds via Transfer Hydrogenation: From Methodology Development to Natural Product Synthesis

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The University of Texas at Austin, 2013

Supervisor: Michael J. Krische

Under the conditions of transfer hydrogenation employing *ortho*-cyclometallated iridium *C*,*O*-benzoate catalysts, selective silylallylation and CF_3-allylation were developed. In both cases, high levels of catalyst-directed enantioselectivity and diastereoselectivity were observed. Column chromatography was then tested as a new protocol to purify the iridium precatalyst; this single component precatalyst was proved to be more efficient to promote carbonyl crotylation reactions, both diastereo- and enantioselectivity were increased. Then, double asymmetric crotylation of 1,3-diols to deliver (pseudo-)C_2-symmetric adducts with exceptional level of enantioselectivity was devised. Implementation of this methodology and other hydrogenative C-C bond formations proved to be effective means for the preparation of two known polypropionate natural product fragments of C19-C25 of scytophycin C, C19-C27 of rifamycin S and the total synthesis of 6-deoxyerythronolide B.

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CHAPTER 1: SYNTHETIC EFFORTS TOWARDS ERYTHRONOLIDE FAMILY NATURAL PRODUCTS

1.1 INTRODUCTION

The erythromycins are a family of polypropinate natural products originally isolated from soil bacterial *Streptomyces erythreus* by Eli Lily back to 1952.[1] It was the first comertialized macrolide antibiotic, which was used for the treatment of numerous infections including, but not limited to, *pneumonia*, *conjunctivitis*, and *erythrasma*.[2] Besides itself, several other semi-synthetic macrolide antibiotics were developed based on the 14-membered lactone motif by different companies.

The structures of the erythromycins were determined by a combination of single-crystal X-ray diffraction analysis and/or a series of detailed degradation analyses.[3,4] All erythromycins share several distinctive architectural features, including a 14-membered macrolactone, glycosidic linkages at C3 and C5, and polyoxygenated backbone. Members of the erythromycin family are differentiated structurally through the absence of hydroxy substituents at the C6 and C12 positions and 6-deoxysugar substituent at C3 and C5 positions. In the later case, the name “erythronolide” was used which referring to the polypropinate derived aglycone (Figure 1.1.1).

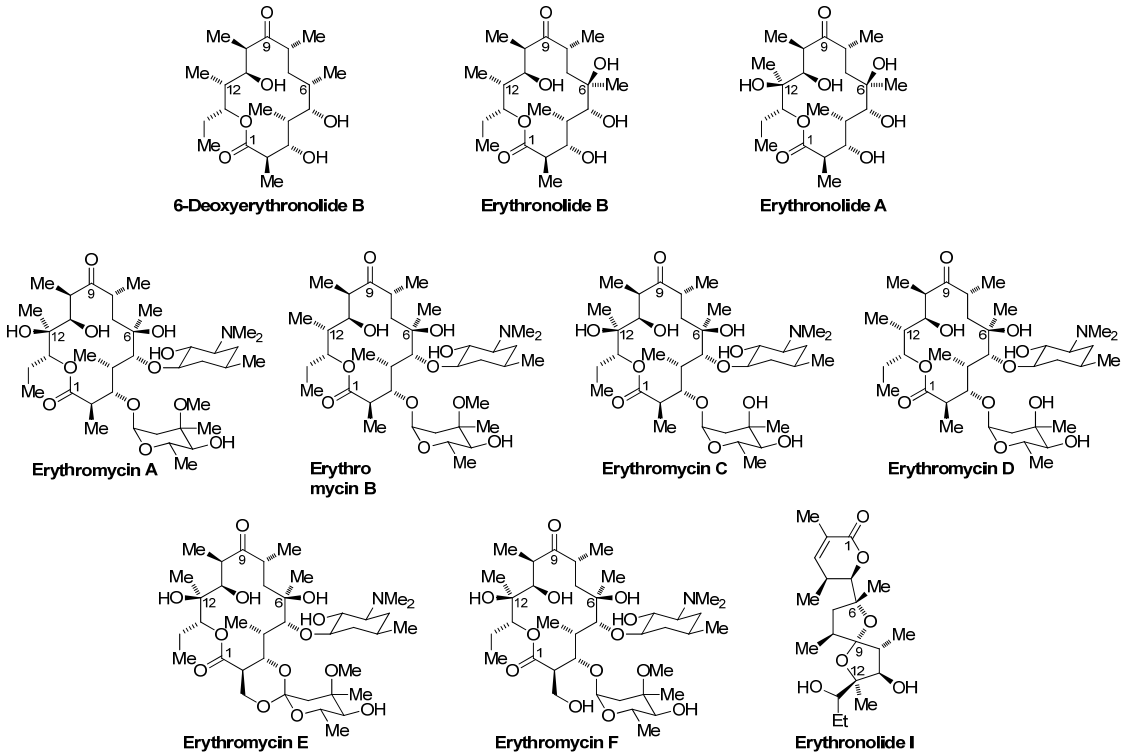


Figure 1.1.1: Selected erythromycin family members.

Biogenically, all the erythromycins came from a same precursor, 6-deoxyerythronolide B. Scientists named this family of natural products polypropionates because they were synthesized through sequential aldol condensation reaction of propionates in the bacterial. Biosynthetic mechanism of the erythromycins constituted the majority of our understanding on the biogenic origin of polyketides. The first polyketide synthase genome sequenced was 6-deoxyerythronolide B synthase (DEBS); many other *Streptomyces* synthases sequenced thereafter proved to be both structurally and functionally similar to DEBS (Figure 1.1.2).[5,6,7]

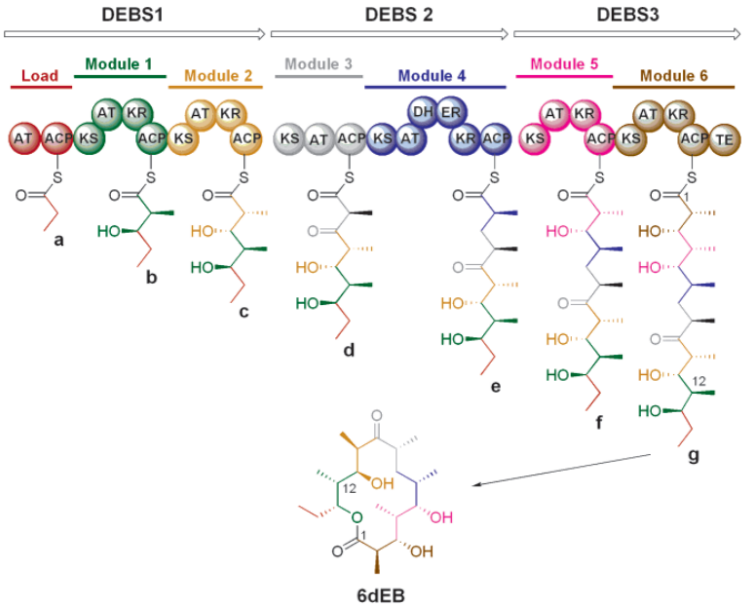
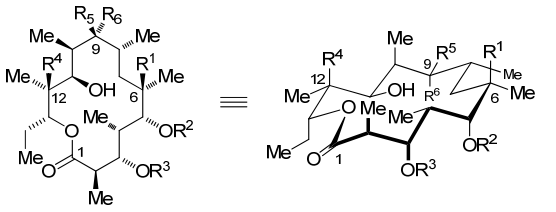


Figure 1.1.2: Proposed biosynthetic scheme of 6-deoxyerythronolide B, figure was copied from Cane, *Nature*, **1995**, *378*, 263.

Erythromycins and erythronolides were iconic synthetic targets for synthetic community. This 14-membered lactone was an inspiration for discovering new synthetic methods with wide applications. In 1956, R. B. Woodward first acknowledged the synthetic chanllenge of the erythromycins by stating "*Erythromycin, with all of our advantages, looks at present time quite hopelessly complex, particularly in view of its plethora of asymmetric centers.*"[8] This statement fueled the synthetic community to pursue this family of natural products. Ever since E. J. Corey's first synthetic work of erythronolide B in 1978, erythromycin family was "*probably the most extensive single project in the history of synthetic organic chemistry*" (Figure 1.1.3).



Erythromycin A, R^1 = OH, R^2 = β-D-desosamine, R^3 = α-D-cladinose, R^4 = OH, R^5 = R^6 = O
Woodward 1981, 54 Steps (LLS), 62 Steps (TS)

Erythromycin B, R^1 = OH, R^2 = β-D-desosamine, R^3 = α-D-cladinose, R^4 = H, R^5 = R^6 = O
Martin 1997, 28 Steps (LLS), 33 Steps (TS)

Erythronolide A, R^1 = OH, R^2 = H, R^3 = H, R^4 = OH, R^5 = R^6 = O
Corey 1979, 39 Steps (LLS), 50 Steps (TS)
Kinoshita 1989, 47 Steps (LLS), 71 Steps (TS)
Carreira 2005, 26 Steps (LLS), 36 Steps (TS)

Erythronolide B, R^1 = OH, R^2 = H, R^3 = H, R^4 = H, R^5 = R^6 = O
Corey 1978, 33 Steps (LLS), 47 Steps (TS)
Kochetkov 1987, 36 Steps (LLS), 51 Steps (TS)
Mulzer 1991, 27 Steps (LLS), 41 Steps (TS)

(*9S*)-Dihydroerythronolide A, R^1 = OH, R^2 = H, R^3 = H, R^4 = OH R^5 = OH, R^6 = H
Stork 1987, 33 Steps (LLS), 46 Steps (TS)
Yonemitsu 1987, 39 Steps (LLS), 63 Steps (TS)
Paterson 1989, 23 Steps (LLS), 28 Steps (TS)
Hoffmann 1993, 27 Steps (LLS), 31 Steps (TS)
Woerpel 2003, 30 Steps (LLS), 31 Steps (TS)

6-Deoxyerythronolide B, R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5 = R^6 = O
Masamune 1981, 26 Steps (LLS), 44 Steps (TS)
Danishefsky 1990, 39 Steps (LLS), 39 Steps (TS)
Evans 1997, 20 Steps (LLS), 27 Steps (TS)
White 2009, 23 Steps (LLS), 25 Steps (TS)

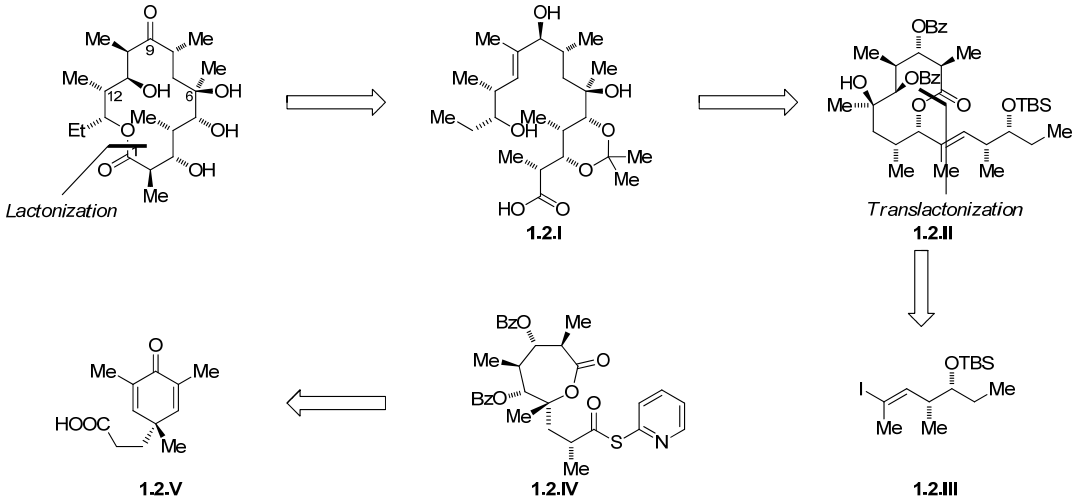
Figure 1.1.3: Summary of steps count for previous total synthesis effort towards erythromycin family natural products.

Due to the space limit, not every single synthesis of each member of erythromycin family will be covered in this review; instead, one of each member will be discussed in details. Graphic summaries of all the previous completed total and formal synthesises will be provided at the end of the chapter.

1.2 ERYTHRONOLIDE B BY COREY (1978)

1.2.1 RETROSYNTHETIC ANALYSIS

In 1978, Corey and coworkers reported their synthesis of erythronolide B, the first total synthesis of any erythromycin family natural products.[9] As shown in Scheme 1.2.1, in their strategy, the 14-membered macrolide in erythronolide B was assembled through Corey-Nicolaou macrolactonization of the corresponding *seco*-acid **1.2.I**, which itself was prepared from an intramolecular translactonization of **1.2.II**. Installation of the vinyl side chain into **1.2.IV** was achieved by a thioester alkylation with vinyl iodide **1.2.III**. Notably, both **1.2.III** and **1.2.IV** fragments were synthesized as a racemic mixture; chiral resolution manipulations were needed to optain enantiopure material.

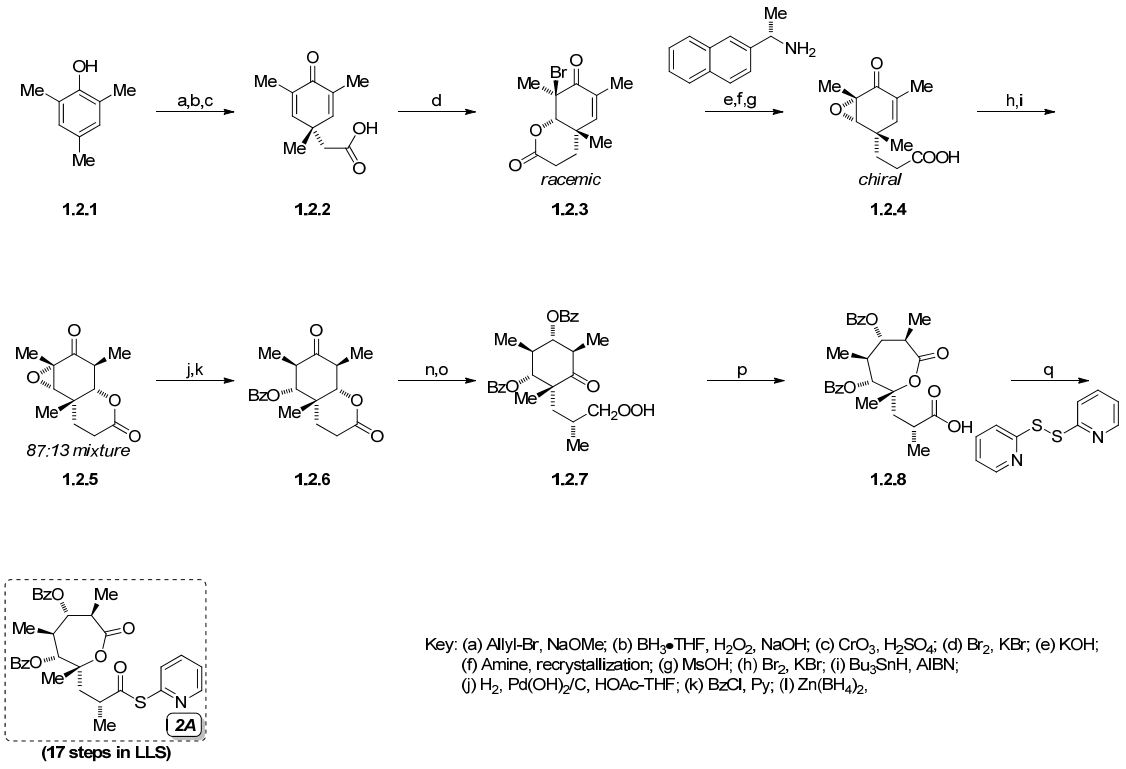


Scheme 1.2.1: Corey's retrosynthetic strategy for erythronolide B.

1.2.2 SYNTHETIC ROUTE

Preparation of fragment **2A** started from dearomatization of phenol **1.2.1**, bromolactonization of **1.2.2** fowllowed by recrystallization with chiral amine base

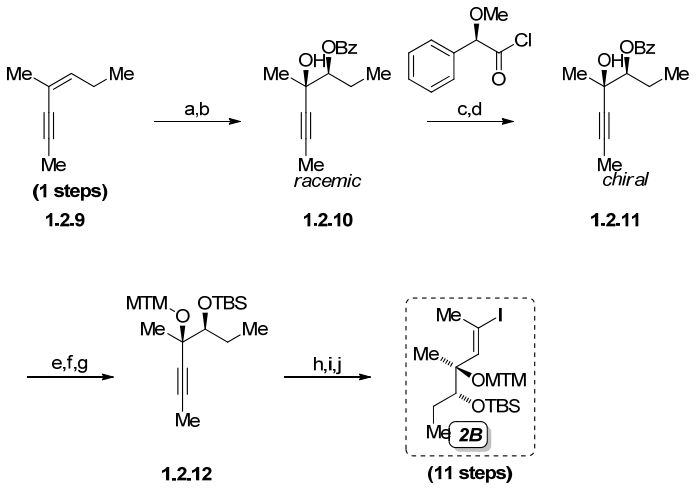
provided enantiomeric pure form of **1.2.3**, which was the precursor of the epoxide **1.2.4**. A second round bromolactonization followed by dehalogenation generated a fully substituted cyclohexanone **1.2.5**. Treatment of **1.2.5** under Baeyer-Villiger oxidation condition provide seven-membered lactone **1.2.8**, which was activated by forming thio-ester **2A** and ready to couple with the other fragment (Scheme 1.2.2).



Scheme 1.2.2: Fragment **2A** synthesis.

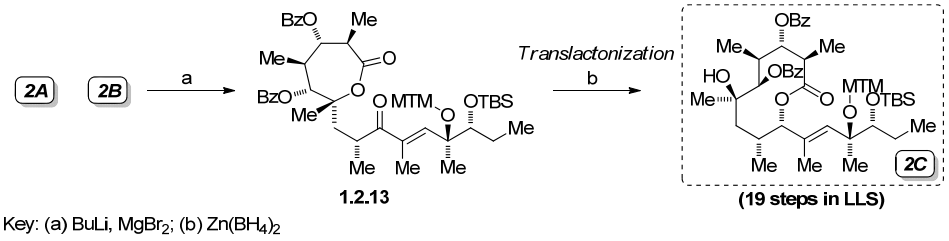
The iodide **2B** was made from enyne **1.2.9**. Chemoselective dihydroxylation followed by a two-step resolution through forming chiral mandelic ester provided chiral tertiary alcohol **1.2.11**. After subsequent mercuration and iodination, the iodide **2B** was

obtained in 11 steps (Scheme 1.2.3). Fragment union was achieved through acylating the vinyl lithium reagent generated from **2B** via lithium-halogen exchange. After transfer lactonization of coupling product **1.2.13**, 10-membered lactone **2C** was obtained, with majority of chiral centers from the natural product setted across the carbon backbone (Scheme 1.2.4).



Key: (a) NMO, OsO_4, THF-H_2O; (b) BzCl, Py; (c) DMAP; (d) water associate P_{500}; (e) Ac_2O, DMSO, HOAc; (f) KOH, H_2O, MeOH; (g) TBSCl, DMAP, DMF; (h) Cy_2BH, then Et_3NO; (i) $Hg(OAc)_2$, NaCl; (j) I_2, Py

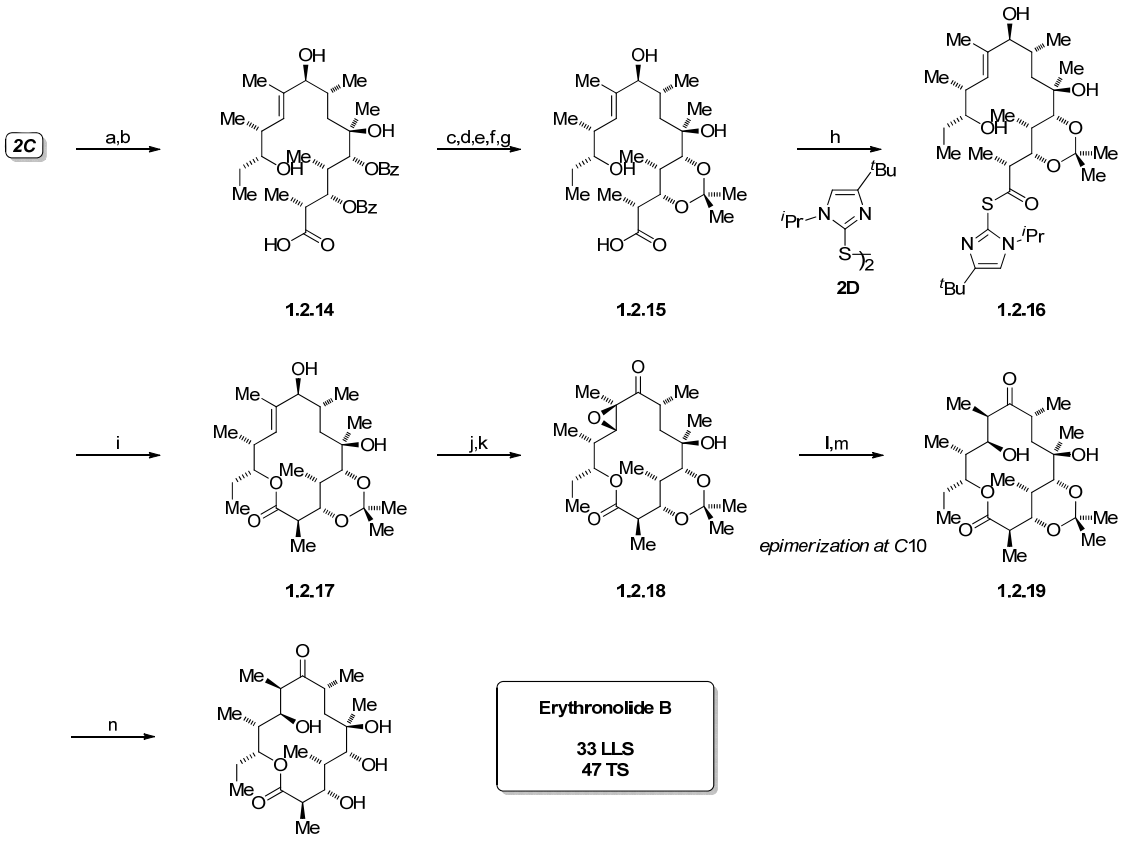
Scheme 1.2.3: Fragment **2B** synthesis.



Key: (a) BuLi, $MgBr_2$; (b) $Zn(BH_4)_2$

Scheme 1.2.4: Fragment union of **2A** and **2B**.

The end game was carrired out simple and straight forward. **2C** was saponified and the *seco*-acid was activated by treating with disulfide **2D** to form macrolactonization precursor **1.2.16**. Heating this thioester provided the macrocyclization product **1.2.17**; Epoxidation of the double bond followed by allylic oxidation gave **1.2.18**. Ring-opening epoxide provided 10-*epi* form of protected erythronolide B, which isomerized to its thermodynamically stable form when treated with base. Deprotecting acetonide gave the natural product (Scheme 1.2.5).



Key: (a) AcOH; (b) LiOH, H_2O_2; (c) KOH; (d) CH_2N_2; (e) HBr; (f) $Me_2C(OMe)_2$, Amberlite-50; (g) KOH; (h) PPh_3; (i) Heating; (j) MnO_2; (k) H_2O_2, NaOH; (l) H_2, Pd/C; (m) K_2CO_3; (n) HCl

Scheme 1.2.5: End game of Corey's synthesis.

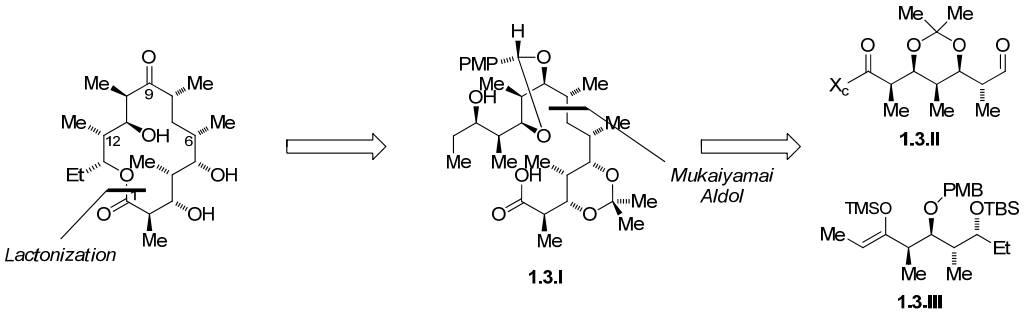
1.2.3 SUMMARY

The landmark first total synthesis of erythronolide B by Corey featured dearomatization, lactone ring expansion, and Corey-Nicolaou macrolactonization.[10] Successful utilizing this lactonization stragegy had a tremendous impact - all subsequent erythromycin family natural products syntheses, except the most recent work published by Krische group,[11] contain the same bond disconnection. The synthesis contained 33 longest linear sequence and 47 total steps. One drawback of Corey's route involved twice chiral resolution and advanced intermediates, which suffered a significant loss of overall yield (less than 0.5%).

1.3 6-DEOXYERYTHRONOLIDE B BY EVANS (1997)

1.3.1 RETROSYNTHETIC ANALYSIS

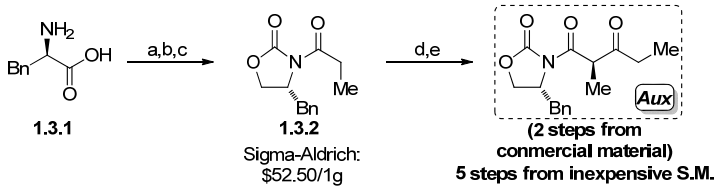
Corey's successful disconnection of erythromycin family at the ester bond and Woodward's extensive model study on the macrolatonization established a doctrine for synthesizing this family of natutal products. All the following synthetic schemes mainly focused on using new methodologies to generate stereotriad and coupling those fragments to form the *seco*-acid. The most successful methodology was Evans aldol chemistry.[12] In 1997, Evans published by far[11] the most concise assembly of erythromycin family natural products using stereoselective aldol reaction.[13] After disconnecting the ester bond, the linear *seco*-acid **1.3.I** could be further disconnected at C7-C8, which provided two equally sized fragments **1.3.II** and **1.3.III**. Both of those two fragments came from a same chiral building blocks synthesized from unnatural amino acid **1.3.1** (Scheme 1.3.1).



Scheme 1.3.1: Evans retrosynthetic analysis.

1.3.2 SYNTHETIC ROUTE

Both fragments of Evans scheme came from same intermediate **Aux**. **Aux** could be made from commercial available oxazolidinone **1.3.2**; however, the prohibitive price for this material normally encouraged synthetic chemistry labs making this compound though a five-step sequence (Scheme 1.3.2).

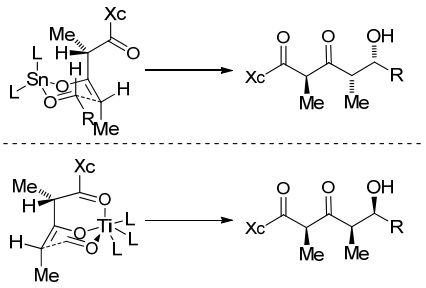


Key: (a) $NaBH_4$, I_2; (b) K_2CO_3, diethyl carbonate; (c) BuLi, then propionyl chloride; (d) Cy_2BOTf, iPr_2NEt, then propionaldehyde; (e) SO_3•Py, TEA, DMSO

Scheme 1.3.2: Common intermediate synthesis.

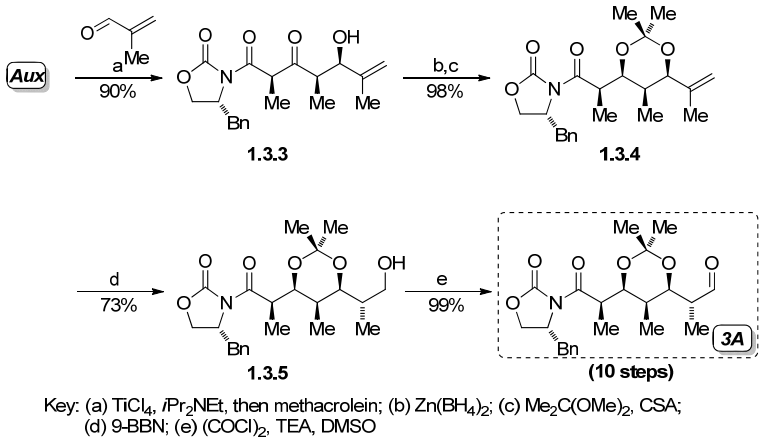
The starting material **Aux** showed excellent level of diastereoselectivity for introducing new chiral centers at the ethyl terminal. Interestingly, changing the Lewis acid core from Sn(II) to Ti(IV) for enolizing the alpha-chiral ketone would also change the stereochemical outcome for the aldol reaction; a mechanistic rationale was attributed to the different coordination ability of Sn(II) and Ti(IV), since Sn(II) normally

coordinated with four monodente ligand, while Ti(IV) would be saturated until six ligands on the metal (Scheme 1.3.3).[14]



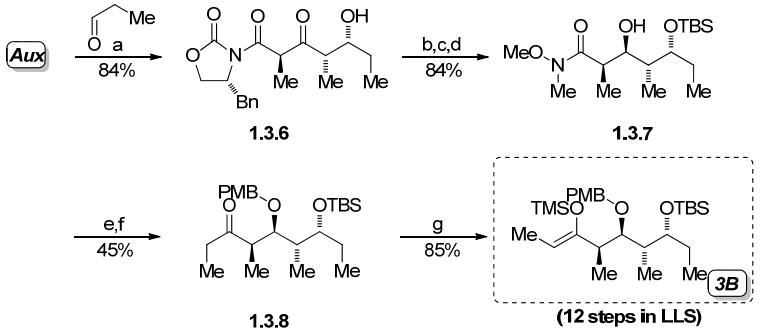
Scheme 1.3.3: Stereochemical outcome of aldol reaction rationale.

Fragment **3A** was synthesized though Ti(IV) mediated aldol reaction of **Aux** with methacrolein. Intramolecular hydride transfer from the chelated zinc intermediate would trigger 1,3-*syn* relationship for the newly generated chiral center. Substrate directed hydroboration-oxidation sequence provided primary alcohol **1.3.5**, which underwent Moffat oxidation to give alpha-chiral aldehyde **3A** (Scheme 1.3.4).



Scheme 1.3.4: Fragment **3A** synthesis.

The other fragment, **3B**, was synthesized through same manner. Using Sn(II) as Lewis acid to enolize the chiral ketone, an *anti* stereochemical outcome was observed. Using $NaBH(OAc)_3$ as external hydride sourse, 1,3-*anti* reduction was achieved and generated the remaining two chiral centers in this fragment. The oxazolidinone motif was replaced with Weinreb amide, followed by mono alkylation to generate alpha-chiral ketone **1.3.8**. Enolization of **1.3.8** with LiHMDS and TMSOTf gave Mukaiyama aldol precursor silyl enol ether **3B** in 12 steps (Scheme 1.3.5).

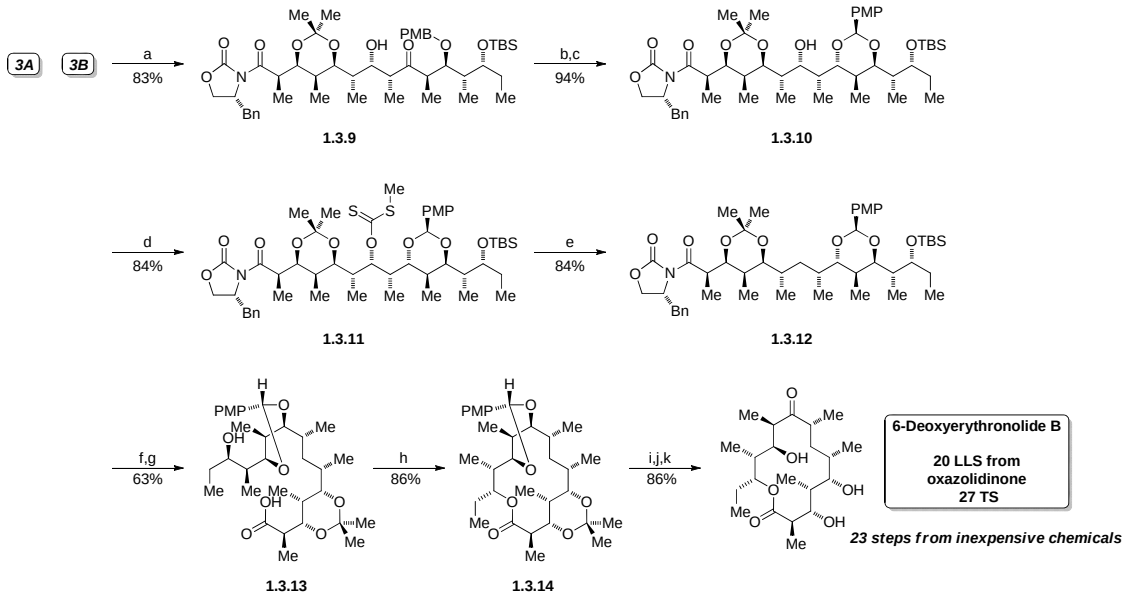


Key: (a) $Sn(OTf)_2$, TEA, then propionaldehyde; (b) $NaBH(OAc)_3$, AcOH; (c) TBSOTf, 2,6-lutidine; (d) $AlMe_3$, (MeO)MeNH•HCl; (e) EtMgBr; (f) $Cl_3CC(NH)O$-(*p*-OMe)Bn, TfOH; (g) BuLi, $(PhMe_2Si)_2NH$, TMSOTf, 2,6-lutidine

Scheme 1.3.5: Fragment **3B** synthesis.

The fragment union was achieved through Mukaiyama aldol reaction. Using BF_3-OEt_2 as Lewis acid, fully substituted stereopolyad **1.3.9** was obtained in 83% yield. The newly generated hydroxyl group needed to be removed to match the structure of the natural product; hence a three-step Barton deoxygenation was carried out. The hydrogen radical labile PMP-acetal motif survived under optimized reaction condition. After hydrogen peroxide facilitated hydrolysis of oxazolidinone auxiliary, the unprotected *seco*-acid **1.3.13** was treated with Yamaguchi lactonization reagent to form macrolactone **1.3.14**. A three-step deprotection sequence, including a Pearlman catalyst promoted

hydrogenolysis of PMP-acetal, PCC mediated site selective oxidation of diol, and acid catalyzed hydrolysis of acetonide, provided the natural product 6-deoxyerythronolide B (Scheme 1.3.6).



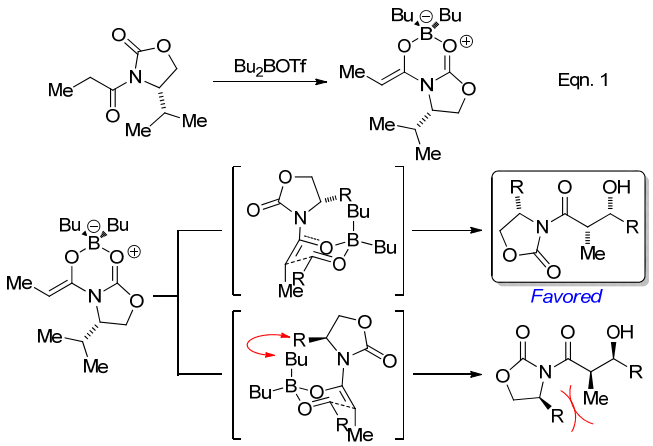
Key: (a) $BF_3 \bullet OEt_2$; (b) $Zn(BH_4)_2$; (c) DDQ; (d) NaH, then CS_2, then MeI; (e) AIBN, Bu_3SnH; (f) LiOOH; (g) TBAF; (h) TEA, 2,4,6-trichlorobenzoyl chloride, then DMAP (i) $Pd(OH)_2/C$, *i*PrOH; (j) PCC; (k) 1M HCl

Scheme 1.3.6: Fragment union and end game for Evans synthesis.

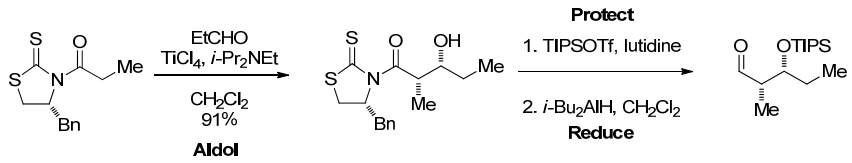
1.3.3 METHODOLOGY HIGHLIGHT

Evans chiral oxazolidinone auxiliary was one of the most utilized auxiliaries; it ccould be easily hydrolized to get ester or acid, or reduced to aldehyde or alcohol. The selectivity for the corresponding aldol reaction was very high for propionate derivatives (eqn. 1, Scheme 1.3.7).[12a] One drawback for Evans aldol reaction was the acetate aldol reaction, normally the selectivity was moderate. Several chiral auxiliaries based on Evans oxazolidinone structure motif were developed in the last three decades to solve this

problem; Crimmins was recently using his own thiazolidinethione auxiliary to synthesize advanced intermediate of Evans total synthesis of 6-deoxyerythronolide B in 24 steps longest linear sequence (Scheme 1.3.8).[15]



Scheme 1.3.7: Stereochemical model for Evans aldol reaction.



Scheme 1.3.8: Example of Crimmins sequence for modified aldol reaction.

1.3.4 SUMMARY

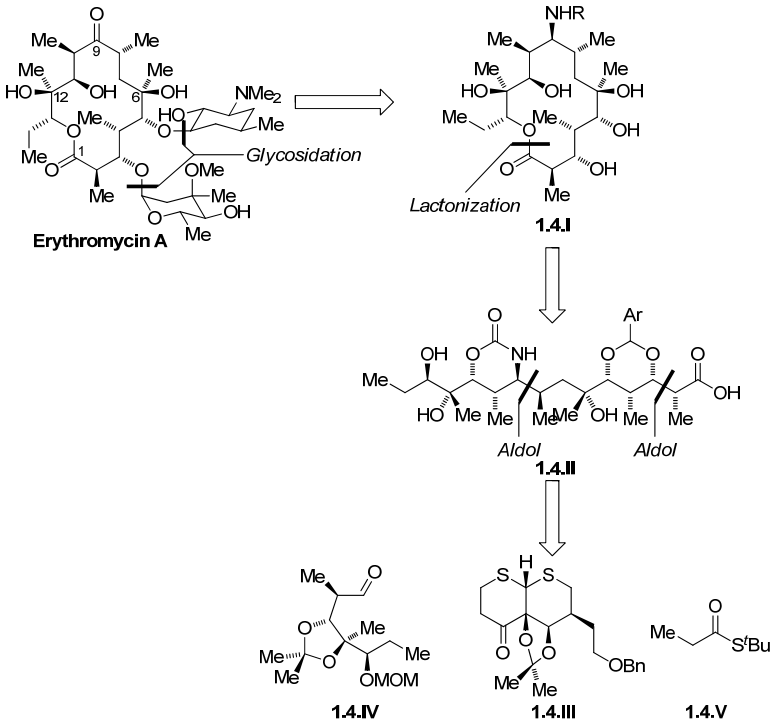
The total synthesis of 6-deoxyerythronolide B still remained as a testing standard for new total synthesis work of erythromycin family natural products. The synthetic scheme was highly convergent; the longest linear sequence was 18 steps from known compound, or 23 steps from inexpensive bulk chemicals. Both fragments could be obtained from a same precursor, which shorten the total steps required to assembly this

molecule. The efficiency to generate chiral centers via Evans aldol reaction was well tested in this synthetic enterprise.

1.4 ERYTHROMYCIN A BY WOODWARD (1981)

1.4.1 RETROSYNTHETIC ANALYSIS

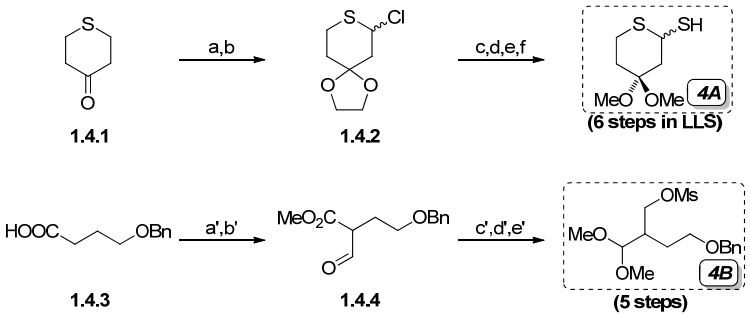
While installing all the chiral centers across the 14-membered lactone ring was already a highly challenging task for synthetic community, glycosidation to introduce two sugar motifs into aglycone of erythromycin proved to be more difficult especially in a site selective fashion. In 1981, Woodward and his group published the first and only total synthesis of erythromycin A.[16] By removing two sugar motifs, the aglycone **1.4.I** was disconnected at the ester bond to provide a second acid **1.4.II**. The stereochemistry of those chiral centers was controlled by a dithiadecalin **1.4.III** as template; the fragments were coupled using aldol reaction (Scheme 1.4.1).



Scheme 1.4.1: Woodward's retrosynthetic analysis.

1.4.2 SYNTHETIC ROUTE

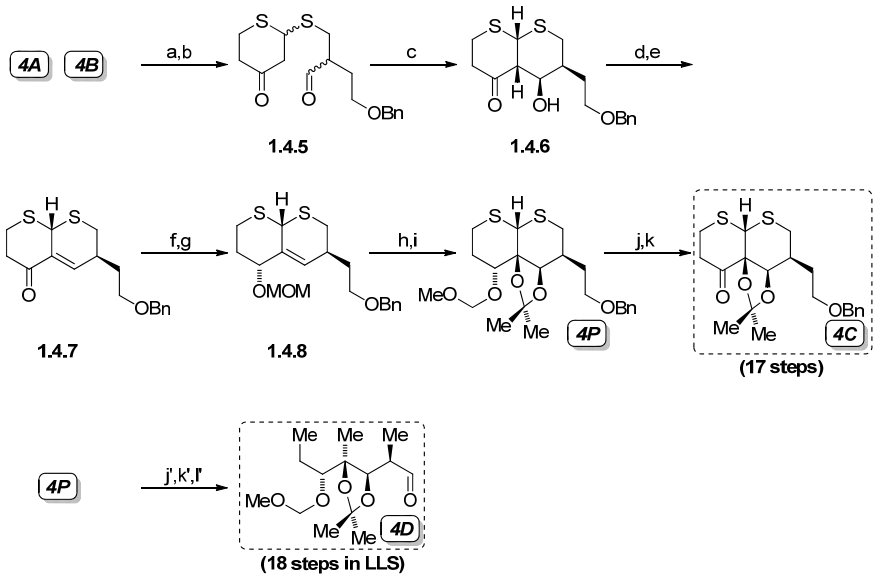
Starting from dihydrothiopyranone **1.4.1**, alpha chlorination with NCS followed by nucleophilic substitution gave **4A** in 6 steps. Carbonylation at the alpha-position of ester generating from acid **1.4.3** provided beta-carbonyl ester **1.4.4**; subsequent manipulations provided **4B** (Scheme 1.4.2).



Key: (a) $HOCH_2CH_2OH$, TsOH; (b) NCS; (c) thiourea; (d) aq. NaOH; (e) aq. HCl; (f) $HC(OMe)_3$, TsOH
(a') conc. H_2SO_4, MeOH; (b') HCOOH, LDA; (c') conc. H_2SO_4, MeOH; (d') LAH; (e') MsCl, Py

Scheme 1.4.2: Dithiadecalin precursors synthesis.

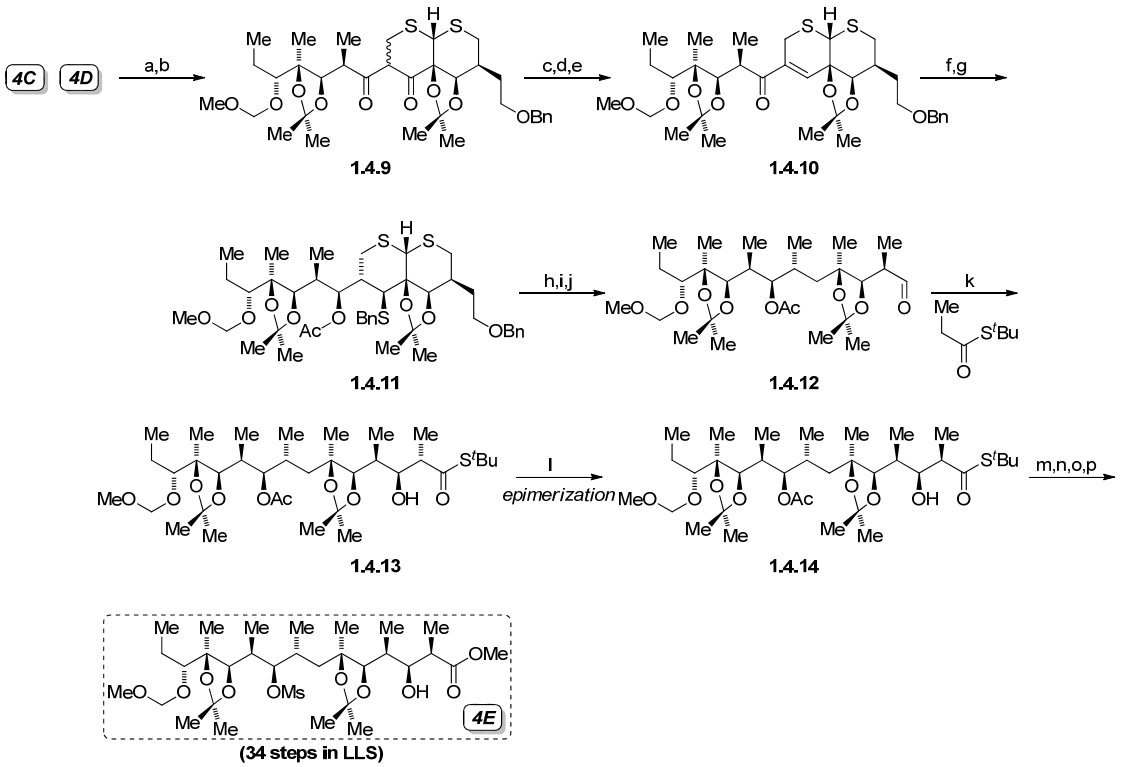
Alkylation of **4B** at the mesylate terminal coupled **4A** and **4B** together as the precursor for the dithiadecalin. A proline catalyzed intramolecular aldol reaction, which was so-called Harjos-Parrish reaction, was carried out to generate **1.4.6**. Beta-hydroxyl dehydration followed by stereoselective carbonyl reduction and further elaboration provided the common intermediate **4P**; successfully identifying this piece as a repeating unit in the molecule helped to reduce the total steps count for erythromycin A synthesis. After desulforation with Raney-Ni, alpha-chiral aldehyde **4D** was obtained in 18 steps (Scheme 1.4.3).



Key: (a) NaH, DMSO; (b) AcOH; (c) D-Proline; (d) MsCl, Py; (e) alumina, EtOH; (f) $NaBH_4$; (g) MOMI, KH; (h) OsO_4, $NaHSO_4$, Py; (i) $Me_2C(OMe)_2$, TsOH; (j) TFA; (k) TFAA, DMSO (j') Raney-Ni, H_2; (k') *o*-$NO_2C_6H_4SeCN$, PBu_3, then H_2O_2; (l') O_3, then Me_2S

Scheme 1.4.3: Dithiadecalin as the template to control stereochemistry.

4C and **4D** were coupled though carbonyl alkylation followed by oxidation to form 1,3-dicarbonyl compound **1.4.9**. A three-step sequence was used to site-selectively remove oxygen on more stereically hindered dithiadecalin motif and generated alpha,beta-unsaturated ketone **1.4.10**. Benzyl thiol was added to this enone motif from the canvex face of the ring system, which helped to define the stereochemistry at C8 of **1.4.11**. Subsequent desulforation and aldol reaction with thioester generated all the carbon skeleton of the *seco*-acid. Substrate steering isomerization promoted by base corrected the stereochemistry at C2 position of **1.4.14**. Suponification of thioester and acetate followed by esterification provided the key intermediate **4E** in 34 steps (Scheme 1.4.4, Figure 1.4.1).



Key: (a) mesityl-Li; (b) TFAA, DMSO, iPr_2NEt; (c) KH, AcCl; (d) $NaBH_4$; (e) MsCl, Py; (f) BnSH, BuLi; (g) LAH; (h) Raney-Ni, H_2; (i) $o\text{-}NO_2C_6H_4SeCN$, PBu_3, then H_2O_2; (j) O_3, then Me_2S; (k) LDA; (l) tBuLi, then AcOH; (m) Na_2CO_3; (n) Bz_2O, Py; (o) MsCl, Py; (p) LiOH, H_2O_2

Scheme 1.4.4: Seco ester **4E** synthesis.

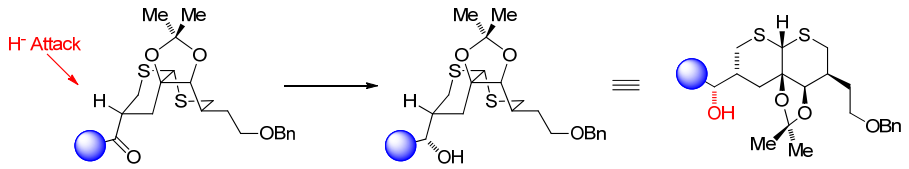
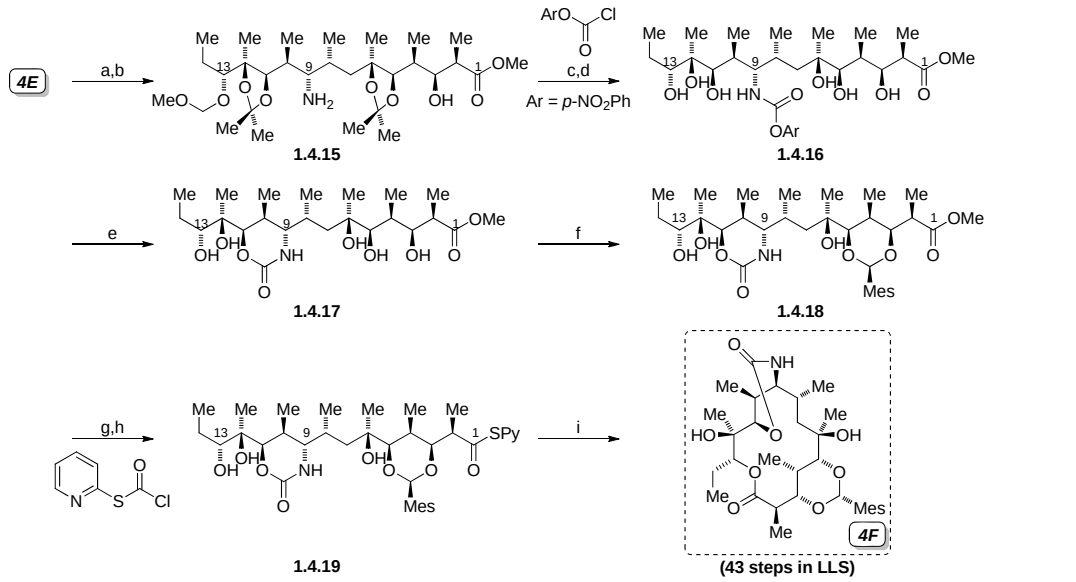


Figure 1.4.1: Dithiadecalin directed face selective reduction of ketone.

Although there were previous example using macrocyclization to construct the lacone motif of erythromycin family natural products before,[17] Woodward provided a first systematic study on the transannular steric effect for assemblying this specific molecule. He proposed a well-accepted doctrine based on extensive experimental studies

of different model systems, that in order to form the ring, C9 must be S configuration and both C9-C11 and C3-C5 sopposed to be protected by cyclic protecting groups such as acetonide and/or carbonate. In order to match the stereochemical requirement for the macrocyclization, mesylate on C9 was replaced with amine to invert the stereochemistry. After protecting C9-C11 with carbamate and C3-C5 with acetal, the seco ester **1.4.18** was suponified and the corresponding acid was activated with thio chloroformate to form thioester, which cyclize upon heating and treating with PPh_3 to form macrocyclic compound **4F** (Scheme 1.4.5).

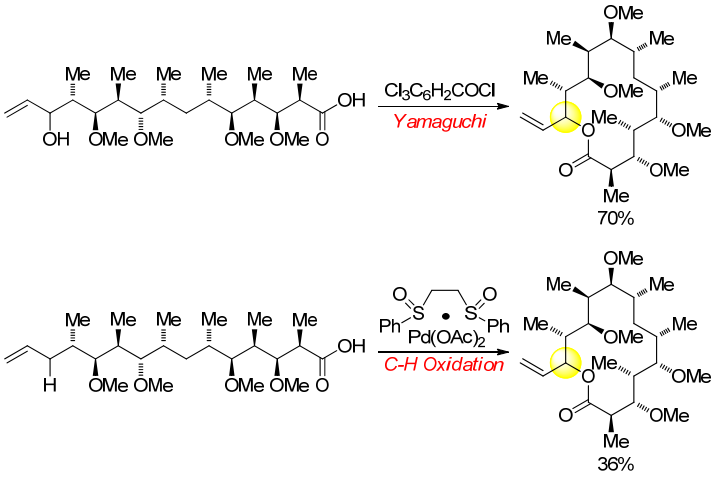


Key: (a) LiN_3, HMPA; (b) PtO_2, H_2; (c) Na_2CO_3; (d) NH_2OH-HCl, KH_2PO_4; (e) TEA; (f) meityl-$CH(OMe)_2$, CSA; (g) EtSH,BuLi, HMPA; (h) TEA; (i) PPh_3, heat

Scheme 1.4.5: Macrocyclization and Woodward's doctrine.

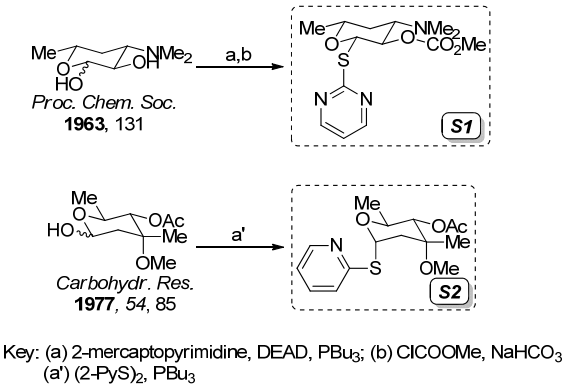
While the idea that preorganization was required for macrocylization was accepted by the synthetic community for nearly three decades, there were exceptions in

the literature. In 1995, Danishefsky published a synthetic work towards 6-deoxyerythronolide B; although the stereochemical requirement matched with Woodward's statement, the macrocyclization only provided 18% yield.[18] In 1997, Martin reported the first and only total synthesis of erythromycin B. In this study, C3-C5 dihydroxyl motif was not protected as cyclic precursor, but the macrocyclization went smoothly.[19] In 2011, White restudied this process and conformed that preorganization was not only necessary but even detrimental in certain cases for macrocyclization (Scheme 1.4.6).[20]



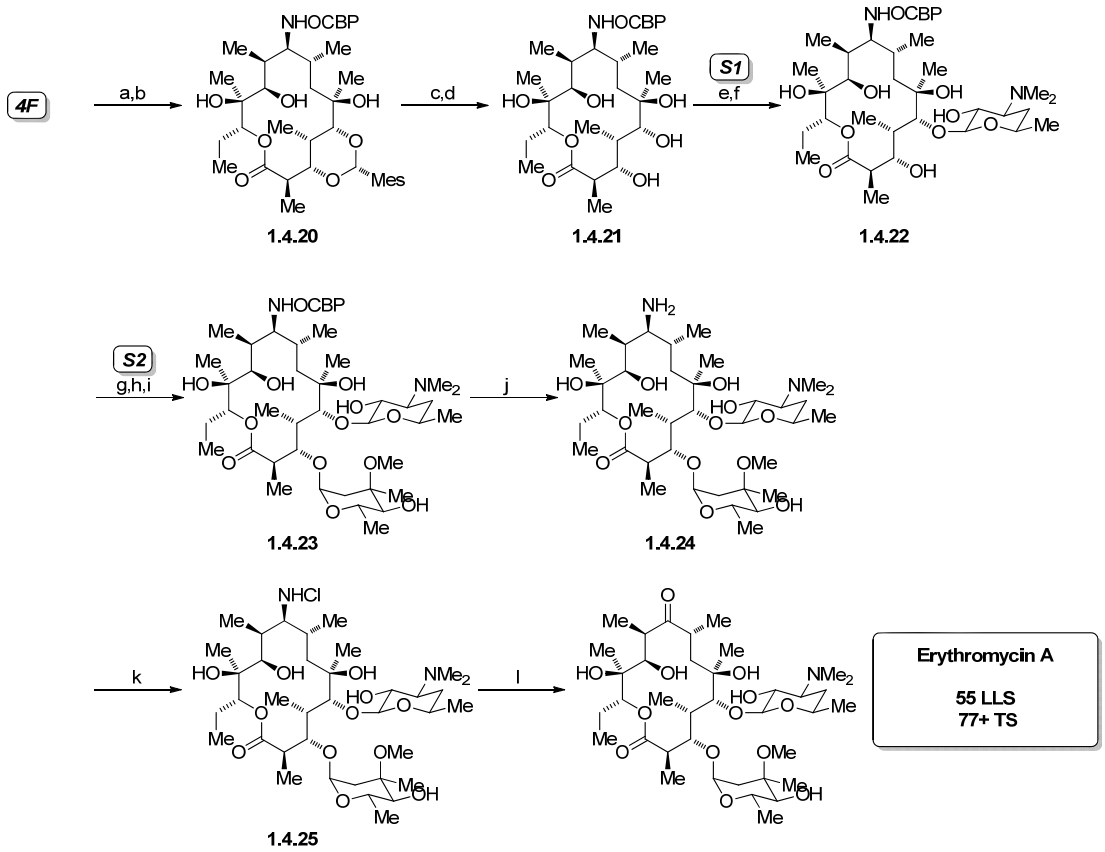
Scheme 1.4.6: White's observation for macrocyclization.

The macrocyclization proved to be challenging for this synthesis; however, the sugar motifs were even more stepy to be made; this was also the normal drawback of making chiral building blocks from sugars, since the polyoxegenated system often suffering from low site-selectivity, hence requiring extensive protection-deprotection manipulations (Scheme 1.4.7).



Scheme 1.4.7: Glycosidation reagent synthesis.

With macrocyclization product **4F** in hand, Woodward attempted the glycosidation. After deprotecting C3-C5 acetal with TFA under buffered condition, region-selective glycosidation with **S1** to penta-ol **1.4.21** was carried out; the reagent became standard glycosidation protocol later. Second-round glycosidation with **S2** provided all the backbone of erythromycin A. This core, **1.4.23**, was further elaborated to introduce carbonyl motif at C9 position in three steps hence finished the first total synthesis of erythromycin (Scheme 1.4.8).



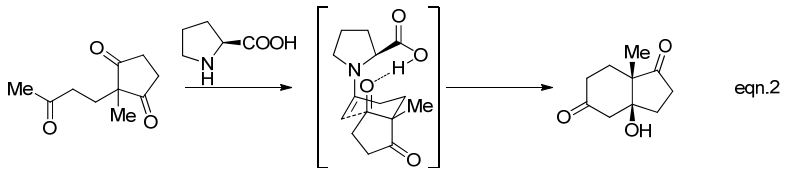
Key: (a) BPCOCl, TEA, DMAP; (b) NaOH, H_2O; (c) SiO_2, aq. TFA; (d) NH_2OH-HCl, KH_2PO_4; (e) AgOTf; (f) MeOH; (g) $ClCO_2Me$, $NaHCO_3$; (h) $Pb(ClO_4)_2$, MeCN; (i) MeOH; (j) Na-Hg/MeOH; (k) NCS, Py; (l) AgF, HMPA

Scheme 1.4.8: Glycosidation and end game for erythromycin A synthesis.

1.4.3 METHODOLOGY HIGHLIGHT

Woodward's synthesis of erythromycin featured the glycosidation and extensive study on preorganization requirement for macrocyclozation, which had been discussed above. Notably, the intramolecular proline catalyzed aldol reaction, which was so-called Harjos-Parrish reaction, was utilized neatly to introduce chirality in the reaction sequence. Harjos reported this reaction back to 1974,[21] and the mechanistic study for the stereochemical outcome was carried out by Houk (Eqn.2).[22] Using congested ring system as template to develop substrate controlled stereochemical introduction was another show

case in this synthetic scheme, for more examples please check a recent review on this topic.[23]



eqn.2

1.4.4 SUMMARY

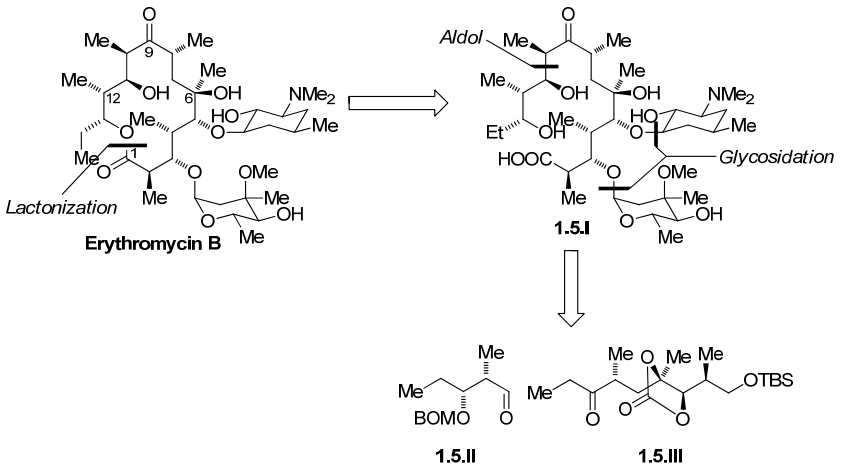
The disconnection strategy of erythromycin in this work was based on identifying repeating stereochemistry assignment in the molecule, and the insight of preorganization provided remarkable consideration to the synthetic community for ring construction. The synthesis was 55 steps longest linear sequence, with overall yield 0.0089%. Glycosidation method was developed in the sequence; however, the last ten steps which were required by glycosidation only provided 1.54% yield. While published two years after Woodward passing away, this synthetic enterprise represented the end of "Woodwardian Era".

1.5 ERYTHROMYCIN B BY MARTIN (1998)

1.5.1 RETROSYNTHETIC ANALYSIS

Erythromycin B, which was the precursor of erythromycin A in soil bacteria fermentation process, was first synthesized by Martin in 1997.[24] The first generation approach was a mimic of biotic synthesizing sequence, which starting from *seco*-acid generation, macrolactonization, and glycosidation to finish the total synthesis. In 2003, Martin published the second generation synthesis of erythromycin;[19] the synthetic scheme

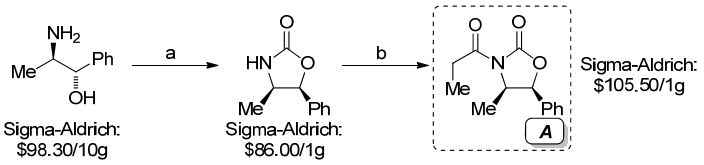
set glycosidation prior to macrolactonization, which in principal would limit protection-deprotection manipulations. Acturally, this new strategy proved to be the most concise total synthesis of erythromycins, to date. In the retrosynthetic analysis, erythromycin was disconnected at the ester bond, which provided a glycosidated *seco*-acid **1.5.I**; further disconnection provided a retro-aldol reaction motif.



Scheme 1.5.1: Retrosynthetic analysis of Martin.

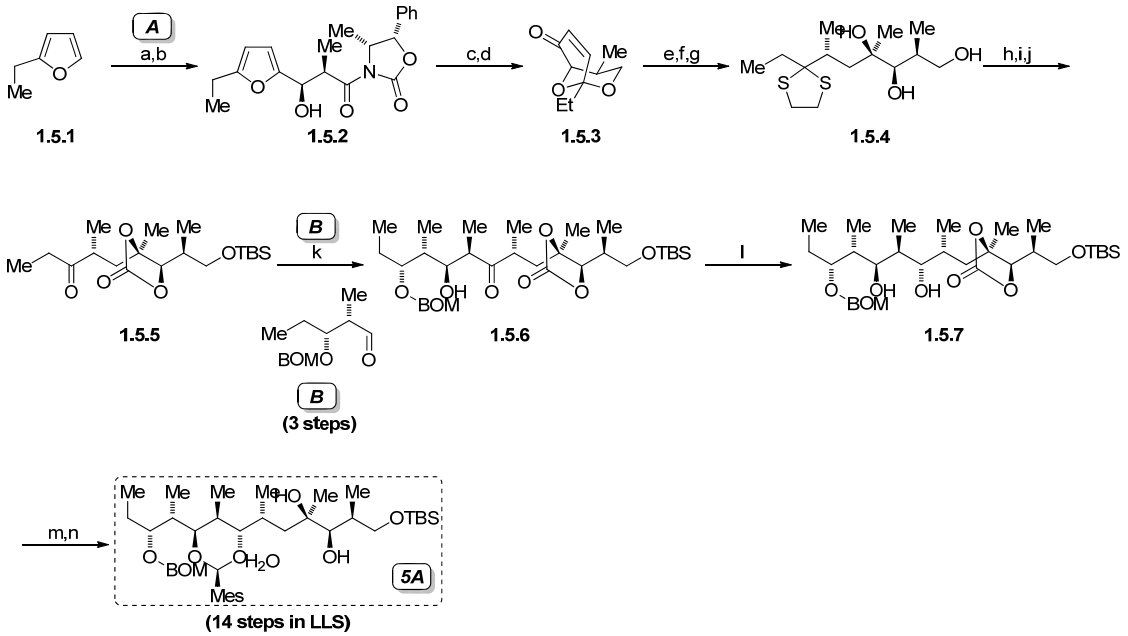
1.5.2 SYNTHETIC ROUTE

The synthetic scheme started with an auxiliary promoted enatioselective aldol reaction towards furyl aldehyde to generate Evans aldol product **1.5.2**. Although this chiral auxiliary was commercial available, the price for it was prohibitive, hence a two steps synthesis of this molecule was necessary in most cases (Scheme 1.5.2).



Scheme 1.5.2: Chiral auxiliary **A** synthesis.

Reductive cleavage of the chiral auxiliary followed by treating the diol with bromine broke the aromaticity of furan to generate [3,3,1]-fused ring system **1.5.3**. Cuperate mediated 1,4-Michael addition followed by cerium promoted carbonyl addition with methium lithium generated substituted dioxabicyclo[3.3.1]nonane, which underwent PPTS promoted ketal opening and dithiane formation wo provide linear stereopolyad **1.5.4**. This strategy was neat and efficient, avoiding using stepy one-dimensional chain elongation strategy which commonly seen in the total synthesis of polyketides. Carbonate protection of 1,2-diol motif and TBS protection of primary hydroxyl group followed by dithiane cleavage generated aldol precursor **1.5.5**. The coupling partner, **B**, which itself needed three steps to make, was reacted with corrospnding lithium enolate of **1.5.5**, through substrate directed carbonyl addition to give fragment union product **1.5.6**. This also provided majority of carbon atoms on the lactone backbone of erythromycin B. Three steps later, glycosidation precursor **5A** was prepared in 14 steps (Scheme 1.5.3).

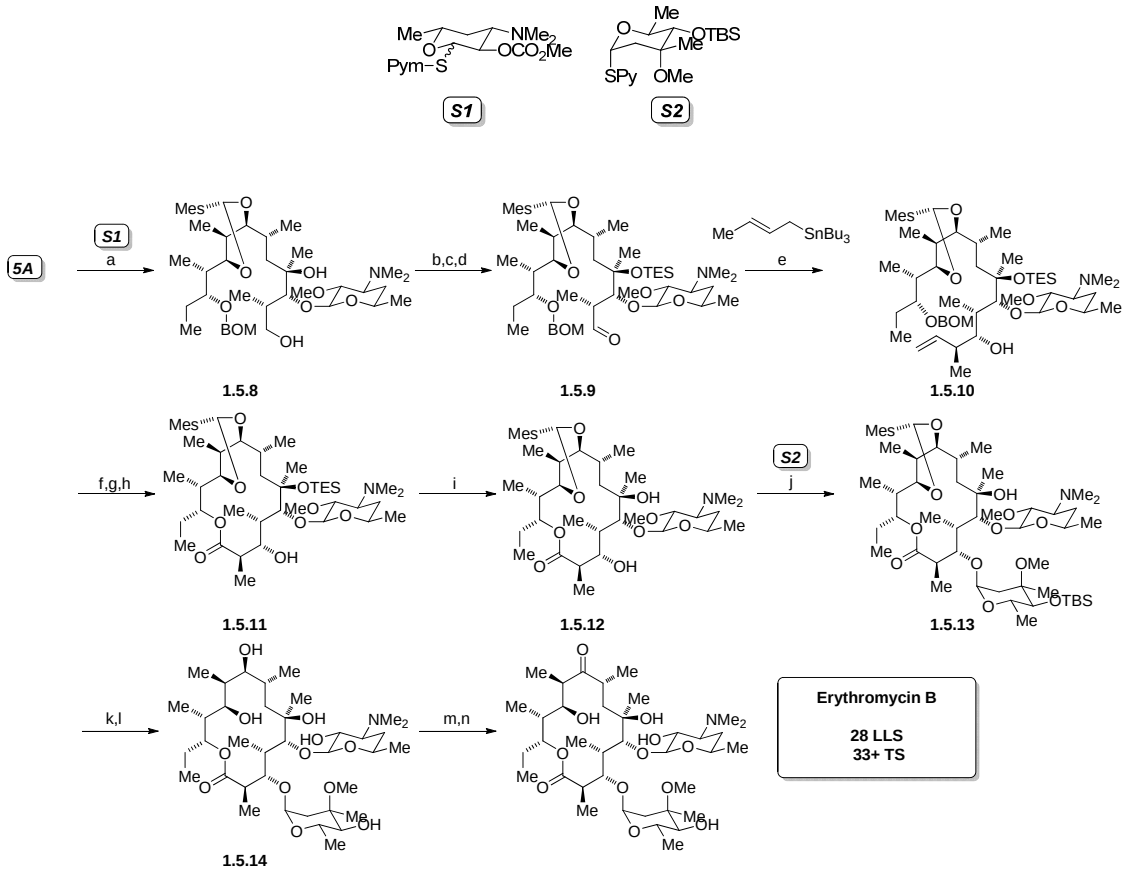


Key: (a) BuLi; (b) Bu_2BOTf; (c) $LiBH_4$; (d) Br_2; (e) $LiCuMe_2$; (f) MeLi-$CeCl_3$; (g) PPTS; (h) TBSCl; (i) CDI; (j) $Hg(ClO_4)_2$, $CaCO_3$; (k) LHMDS; (l) $Me_4NBH(OAc)_3$; (m) $Me_3C_6H_2CH(OMe)_2$, CSA; (n) $LiBH_4$

Scheme 1.5.3: Fragment **5A** synthesis.

Altough not using exactly the same compounds, the glycosidation reagents **S1** and **S2** which Martin used in his total synthesis were quite similar to what Woodward had developed before. In Woodward synthesis, C5-C6 diol could be selectively glycosidated at the C5 position without touching C6 hydroxyl group. However, this selectivity proved to be case dependent, as Martin only observed 1.2:1 ratio favored to the desired one; futurnately, those two regioisomers could be separated easily. After obtaining alpha-chiral aldehyde **1.5.9**, allylstannane mediated Sakurai type crotylation reaction was proceeded to introduce the two last carbon atoms in the *seco*-acid. Oxidative cleavage of olefin **1.5.10** with OsO_4 in DMF generated beta-hydroxyl acid,[25] which underwent Yamaguchi lactonization smoothly to give macrolactone **1.5.11**. It was quite impressive at this step, since the macrolactonization proceeded without matching preorganization

required postulated by Woodward, also the complete selectivity of C13-hydroxyl group over C3-hydroxyl group. The unprotected hydroxyl group reacted with **S2** for the second glycosidation, and the product, **1.5.13**, was only steps away from the final natural product, erythromycin B (Scheme 1.5.4).



Key: (a) AgOTf, 2,6-*t*Bu$_2$Py; (b) TBAF; (c) TESOTf, *i*Pr$_2$NEt; (d) (COCl)$_2$, DMSO, TEA; (e) BF_3-OEt$_2$; (f) OsO_4, Oxone, $NaHCO_3$; (g) Pd/C, $HClO_4$; (h) 2,4,6-trichlorobenzoyl chloride, TEA, then DMAP; (i) TBAF; (j) Cu(OTf)$_2$, CuO; (k) AcOH; (l) TBAF; (m) Dess-Martin Periodate; (n) MeOH, heating

Scheme 1.5.4: Glycosidation and end game.

1.5.3 SUMMARY

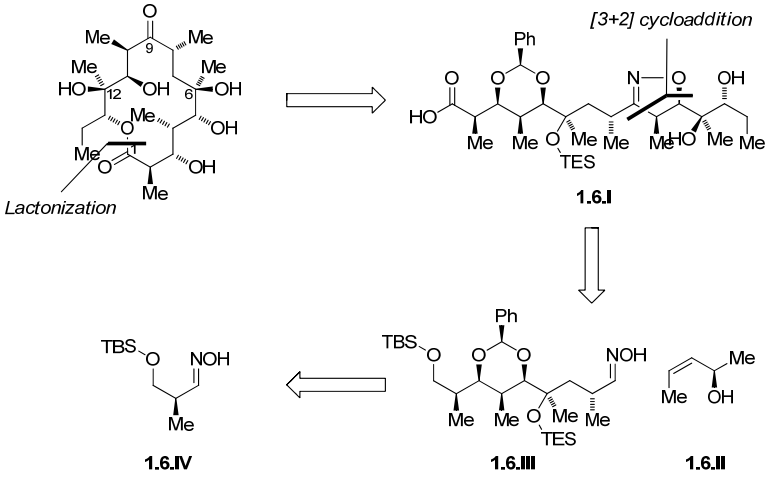
Martin provided two elegant total synthesis schemes of erythromycin B. Both of these two synthesis were featured the application of dearomatization of furan ring, aldol coupling and late stage glycosidations. The second synthesis, which avoiding adopting biomimic synthetic pathway, showed the power of synthetic planning and provided synthetic community an oppoturnity to re-think about well-accepted doctrine of Woodward's postulation. Comparing with Woodward's erythromycin A synthsis, Martin's scheme was much shorter; it was only 28 steps in the longest linear sequence, which was only a half of Woodward's work.

1.6 ERYTHRONOLIDE A BY CARREIRA (2005)

1.6.1 RETROSYNTHETIC ANALYSIS

Unlike erythronolide B and 6-deoxyerythronolide B, erythronolide A, the aglycone form of natural product erythromycin A, was not observed in bacteria culture. Oxidation at the C12 position of erythronolide backbone seemed to be unlikely prior to glycosidation, it was believed that erythromycin A came through oxidation of erythromycin B, which itself came from oxidation at C6 position followed by glycosidation of C3 and C5 hydroxyl groups on the precursor 6-deoxyerythronolide B.[5,6] Although this compound was not isolated from natural, the interesting structure motif of highly oxygenated 14-membered lactone still drew considerable attention from synthetic community; the first total synthesis of erythronolide was carried out by Corey in 1979, right after his landmark first total synthesis of erythronolide B, which required 39 longest linear sequence and 50 total steps.[17a]

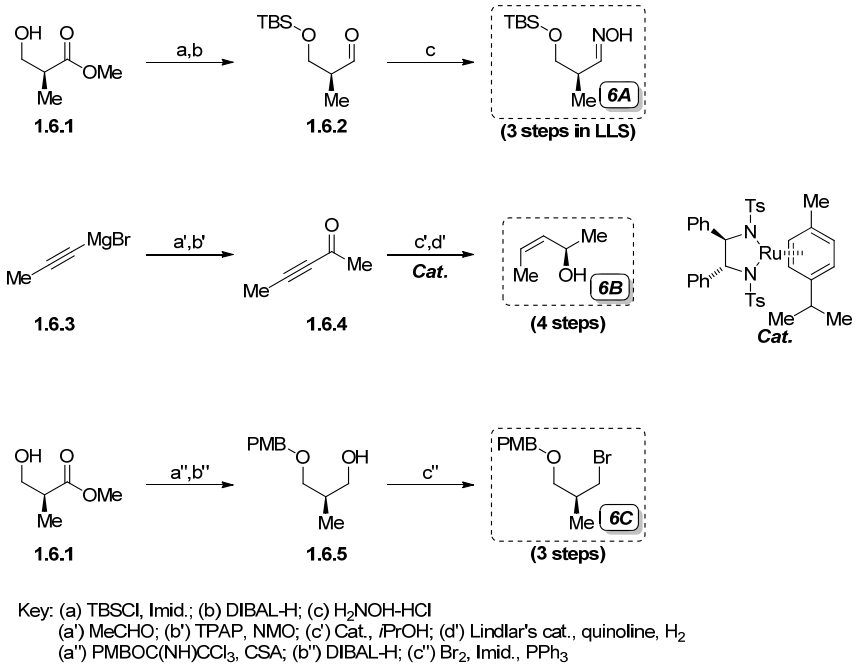
In 2005,[26] Carreira was able to synthesize erythronolide A through iterative utilization of nitrile oxide [3+2] cyclo addition.[27] The 14-membered lactone was disconnected at the ester bond as all the previous work did, to provide the *seco*-acid **1.6.I**. A novel Mg promoted nitrile oxide [3+2] cycloaddition strategy was used to combine two fragments, **1.6.II** and **1.6.III**, together in high yield and selectivity. The nitrile oxide piece **1.6.III** was obtained though another [3+2] cycloaddition from **1.6.IV** (Scheme 1.6.1).



Scheme 1.6.1: Retrosynthetic analysis of Carreira's synthesis.

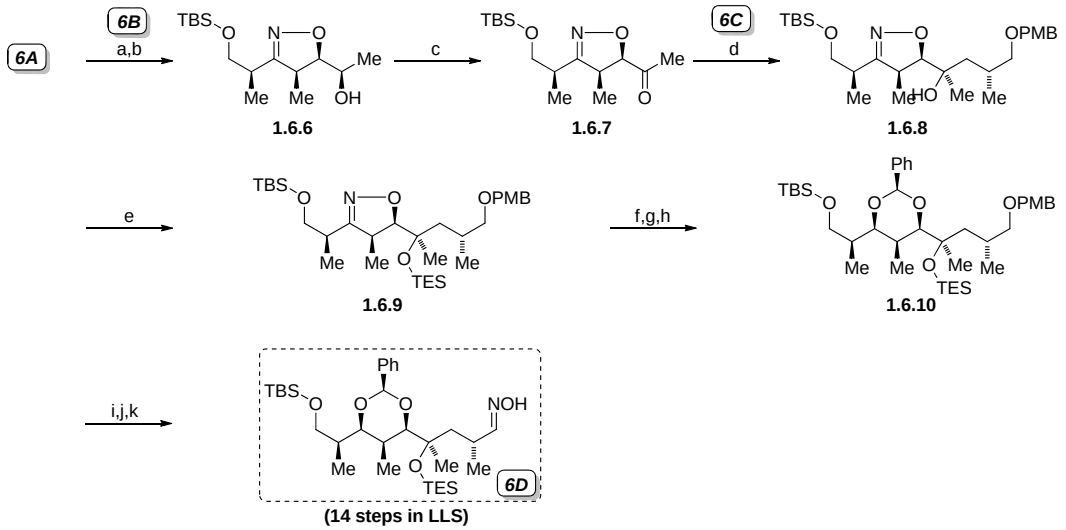
1.6.2 SYNTHETIC ROUTE

The synthesis began with modification of commercial available chiral building block Roche ester **1.6.1**. Synthesis of fragment **6A**, which was in the longest linear sequence of the whole synthetic plan, needed three steps. The coupling partner **6B** was prepared by Noyori asymmetric hydrogenation of acetylenic ketone **1.6.4**. The third piece bromide **6C**, which also came from Roche ester **1.6.1**, was prepared through simple manipulations including PMB protection and bromination (Scheme 1.6.2).



Scheme 1.6.2: Synthesis of fragment **6A**, **6B** and **6C**.

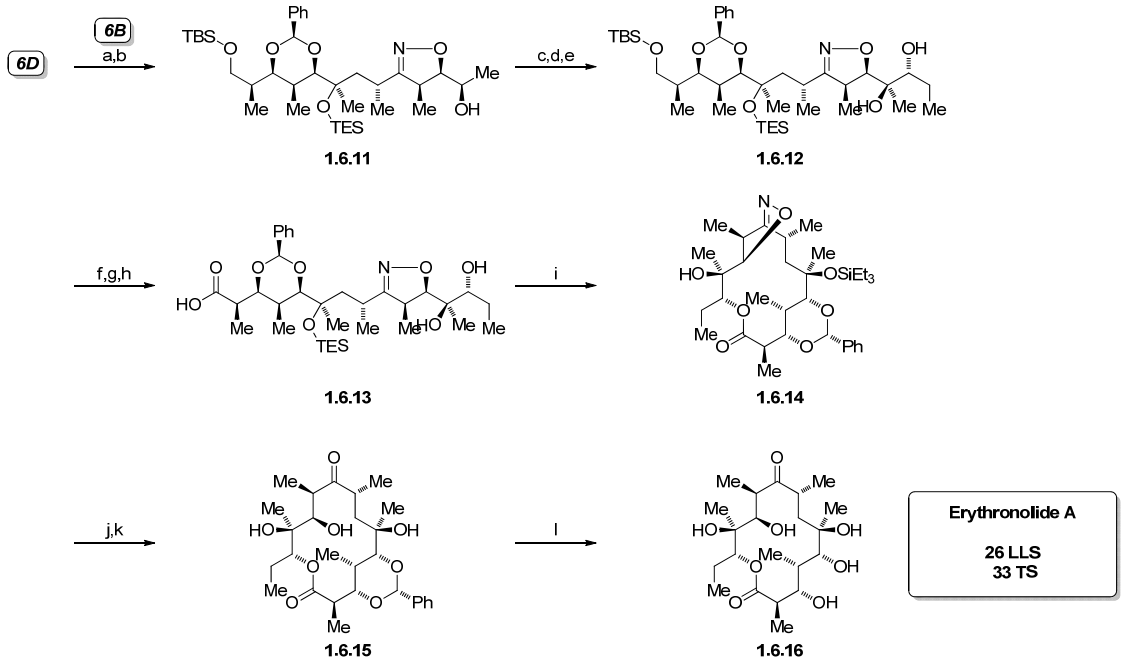
Fragment **6A** underwent smooth Mg-promoted [3+2] cycloaddition with enantiomerically pure allylic alcohol **6B** to form **1.6.6** in good yield and selectivity. Oxidative cleavage followed by carbonyl addition with the Grignard reagent generated from **6C** through Felkin-Anh controled provided stereopolyad **1.6.8**. This tertiary alcohol was also obtained in high diastereoselectivity. Reductive cleavage of the N-O bond in the dihydroisoxazole motif with Raney-Ni followed by zinc borohydride mediated 1,3-induction hydride transfer provided tertiary alkyl silyl ether **1.6.10**; since the highly steric demanding environment where the silyl group sit on, the protecting group was stable in the following manipulations (Scheme 1.6.3).



Key: (a) *t*BuOCl; (b) *i*PrOH, ErMgBr; (c) TPAP, NMO; (d) THF; (e) TESOTf, 2,6-lutidine; (f) Raney-Ni, $B(OH)_3$, H_2; (g) $Zn(BH_4)_2$; (h) $PhCH(OMe)_2$, CSA; (i) DDQ; (j) TEMPO, NaOCl; (k) H_2NOH-HCl, Py

Scheme 1.6.3: Fragment union to generate **6D**.

Fragment **6D** underwent second interative [3+2] cycloaddition with allylic alcohol **6B** to form **1.6.11**; notably, for system as complicated as **6D** and **6B**, this cycloaddition still went smoothly and provided excellent level of diastereoselectivity. Oxidizing the alcohol **1.6.11** to form a ketone, followed by Wittig homologation and stereoselective dihydroxylation provide diol **1.6.12**. Subsequent manipulation including chemoselective oxidation of primary alcohol to form carboxylic acid **1.6.13** and Yamaguchi macrolactonization to close the 14-membered lactone ring **1.6.14**. The dihydroisoxazole motif was reduced followed by $Pd(OAc)_2$ promoted hydrogenolysis of benzylic protecting group provided erythronolide A.



Key: (a) *t*BuOCl; (b) *i*PrOH, ErMgBr; (c) TEMPO, NaOCl, KBr; (d) $PrPPh_3Br$, *t*BuLi; (e) $(DHQD)_2PHAL$, $K_3[Fe(CN)_6]$, $MeSO_3NH_2$, K_2CO_3, K_2OsO_4; (f) HF-Py, Py; (g) TEMPO, NaOCl, KBr; (h) $NaClO_2$, 2-methyl-2-butene; (i) 2,4,6-trichlorobenzoyl chloride, TEA, then DMAP; (j) HF-NEt_3, NEt_3; (k) Raney-Ni, AcOH, H_2; (l) $Pd(OAc)_2$, MeOH, H_2

Scheme 1.6.4: End game of Carreira's synthesis.

1.6.3 METHODOLOGY HIGHLIGHT

Nitrile oxide cycloaddition proved to be a highly selective method in organic synthesis to construct hetereocyclic compounds as masked 1,3-dioxygenated motif. Normally, the solvent polarity had little effect on the regioselectivity; instead, steric effects generally dominated.[28] The first successful metal coordination controled 1,3-dipolar cycloadditions of this type was reported by Kanemasa back to 1994.[29] In 2001, Carriera developed a novel strategy to generate stereopolyad based on Kanemasa's work, and this methodology proved to be very efficient and successful.[27] Ever since the development of this strategy, several polyketide natural products, including epothilone A

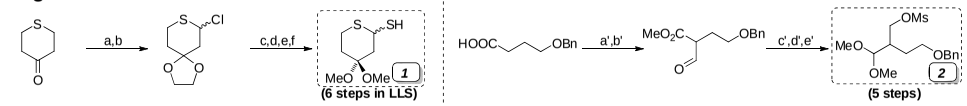
and B,[30] erythronolide A and bafilomycin A,[31] were synthesized by Carriera's group utilizing this methodology.

1.6.4 SUMMARY

Carreira developed the most concised assembly of erythronolide A, the aglycone form of erythromycin A, to date. The synthetic route constituted of 26 steps in longest linear sequence and 33 total steps from Roche ester. The whole synthetic scheme featured iterative application of nitrile oxide [3+2] cycloaddition to control stereochemistry and substrate directed carbonyl addtions. The application of chiral building block Roche ester helped to avoid using stoichmetric amount of chiral auxiliaries, which enhance the atomic economy of the whole synthetic scheme. The efficiency of this [3+2] cycloaddition was also demonstrated in the fragment union step.

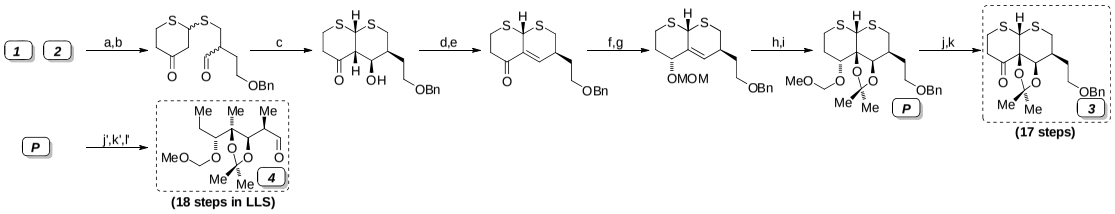
Erythromycin A (Woodward, *J. Am. Chem. Soc.* **1981**, *103*, 3210.)

Fragment 1 and 2



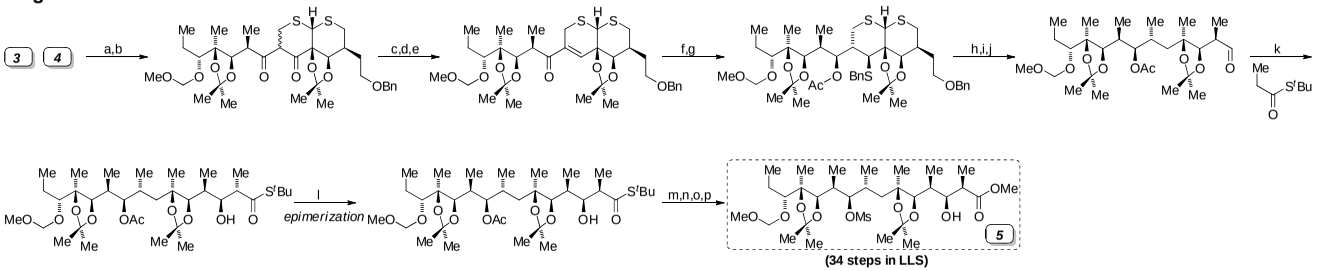
Key: (a) $HOCH_2CH_2OH$, TsOH; (b) NCS; (c) thiourea; (d) aq. NaOH; (e) aq. HCl; (f) $HC(OMe)_3$, TsOH
(a') conc. H_2SO_4, MeOH; (b') HCOOH, LDA; (c') conc. H_2SO_4, MeOH; (d') LAH; (e') MsCl, Py

Fragment Union, Fragment 3 and 4



Key: (a) NaH, DMSO; (b) AcOH; (c) D-Proline; (d) MsCl, Py; (e) alumina, EtOH; (f) $NaBH_4$; (g) MOMI, KH; (h) OsO_4, $NaHSO_4$, Py; (i) $Me_2C(OMe)_2$, TsOH; (j) TFA; (k) TFAA, DMSO
(j') Raney-Ni, H_2; (k') *o*-$NO_2C_6H_4SeCN$, PBu_3, then H_2O_2; (l') O_3, then Me_2S

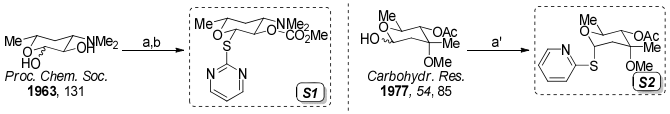
Fragment Union



Key: (a) mesityl-Li; (b) TFAA, DMSO, *i*Pr_2NEt; (c) KH, AcCl; (d) $NaBH_4$; (e) MsCl, Py; (f) BnSH, BuLi; (g) LAH; (h) Raney-Ni, H_2; (i) *o*-$NO_2C_6H_4SeCN$, PBu_3, then H_2O_2; (j) O_3, then Me_2S; (k) LDA; (l) *t*BuLi, then AcOH; (m) Na_2CO_3; (n) Bz_2O, Py; (o) MsCl, Py; (p) LiOH, H_2O_2

Erythromycin A (Woodward, *J. Am. Chem. Soc.* **1981**, *103*, 3210.) (*continued*)

Glycosidating Reagents S1 and S2

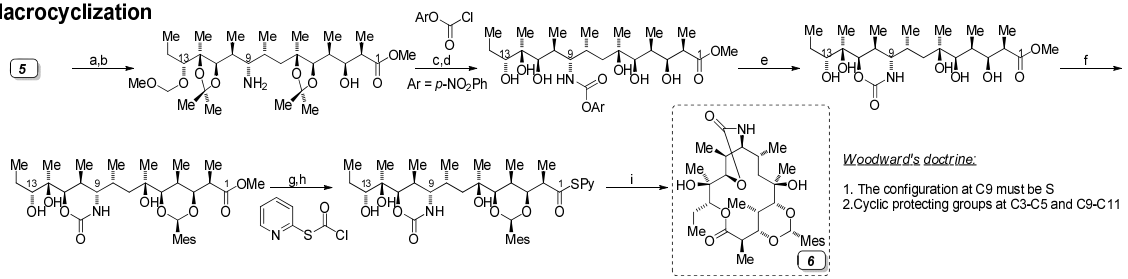


Proc. Chem. Soc. **1963**, 131

Carbohydr. Res. **1977**, *54*, 85

Key: (a) 2-mercaptopyrimidine, DEAD, PBu_3; (b) ClCOOMe, $NaHCO_3$
(a') $(2\text{-PyS})_2$, PBu_3

Macrocyclization

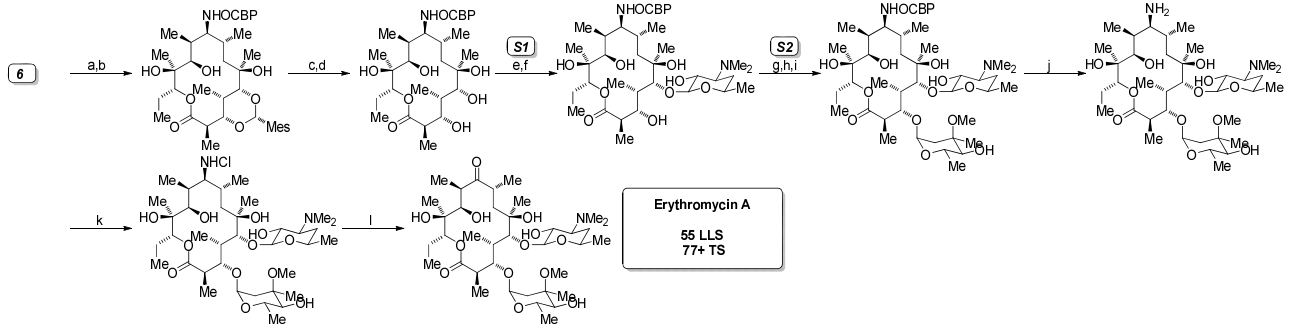


Woodward's doctrine:

1. The configuration at C9 must be S
2.Cyclic protecting groups at C3-C5 and C9-C11

Key: (a) LiN_3, HMPA; (b) PtO_2, H_2; (c) Na_2CO_3; (d) NH_2OH-HCl, KH_2PO_4; (e) TEA; (f) meityl-$CH(OMe)_2$, CSA; (g) EtSH,BuLi, HMPA; (h) TEA; (i) PPh_3, heat

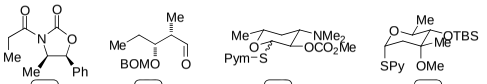
Glycosidation and End Game



Key: (a) BPCOCl, TEA, DMAP; (b) NaOH, H_2O; (c) SiO_2, aq. TFA; (d) NH_2OH-HCl, KH_2PO_4; (e) AgOTf; (f) MeOH; (g) $ClCO_2Me$, $NaHCO_3$; (h) $Pb(ClO_4)_2$, MeCN; (i) MeOH; (j) Na-Hg/MeOH; (k) NCS, Py; (l) AgF, HMPA

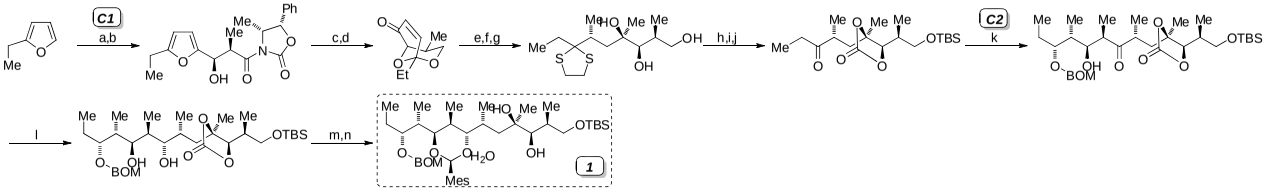
Erythromycin B (Martin, *J. Am. Chem. Soc.* **1997**, *119*, 3193; *Tetrahedron* **2007**, *63*, 5709.)

Chiral Auxiliary and Sugar



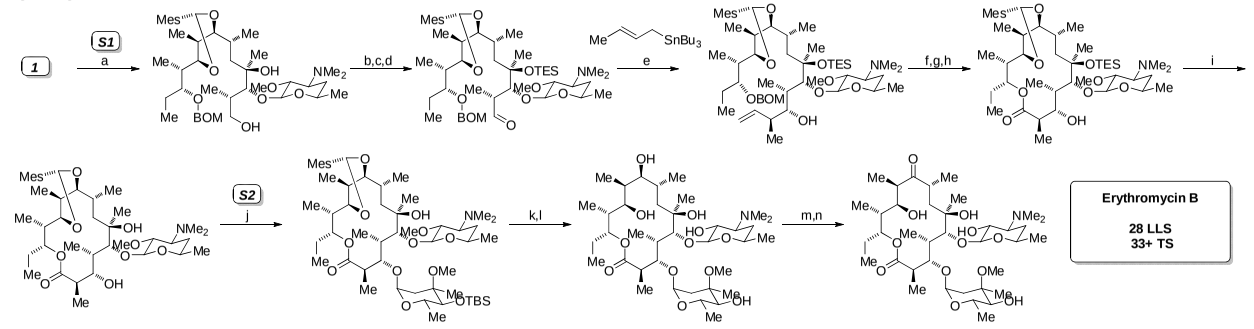
Sigma-Aldrich: $105.50/1g

Functionalization of Furan



Key: (a) BuLi; (b) Bu_2BOTf; (c) $LiBH_4$; (d) Br_2; (e) $LiCuMe_2$; (f) MeLi-$CeCl_3$; (g) PPTS; (h) TBSCl; (i)CDI; (j) $Hg(ClO_4)_2$, $CaCO_3$; (k) LHMDS; (l) $Me_4NBH(OAc)_3$; (m) $Me_3C_6H_2CH(OMe)_2$, CSA; (n) $LiBH_4$

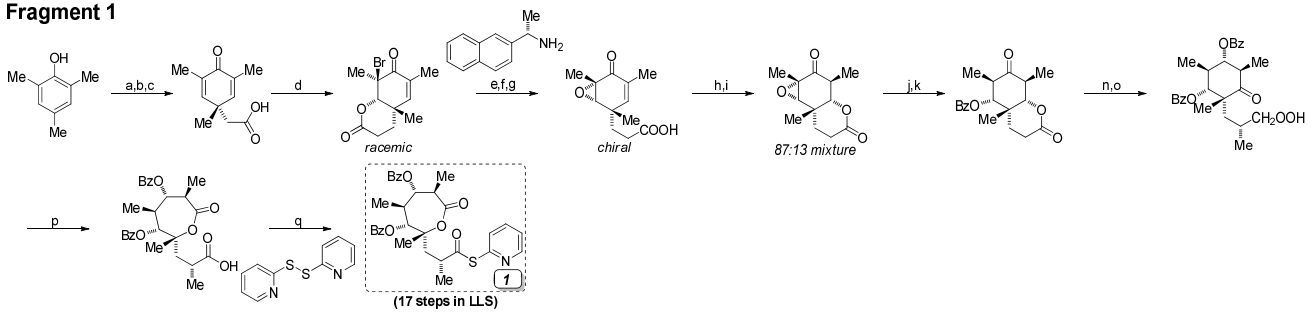
Glycosylation



Key: (a) AgOTf, 2,6-tBu_2Py; (b) TBAF; (c) TESOTf, iPr_2NEt; (d) $(COCl)_2$, DMSO, TEA; (e) BF_3-OEt_2; (f) OsO_4, Oxone, $NaHCO_3$; (g) Pd/C, $HClO_4$; (h) 2,4,6-trichlorobenzoyl chloride, TEA, then DMAP; (i) TBAF; (j) $Cu(OTf)_2$, CuO; (k) AcOH; (l) TBAF; (m) Dess-Martin Periodate; (n) MeOH, heating

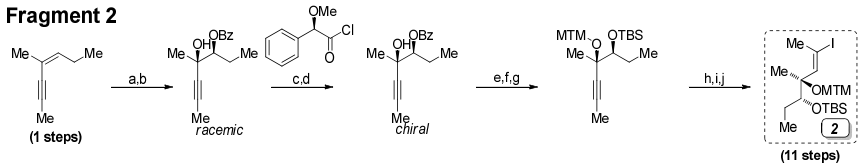
Erythronolide A (Corey, *J. Am. Chem. Soc.* **1979**, *101*, 7131.)

Fragment 1



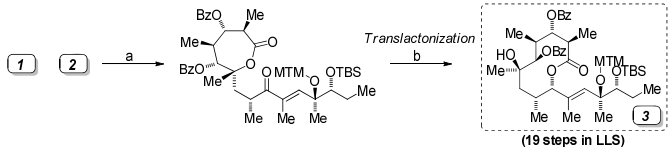
Key: (a) Allyl-Br, NaOMe; (b) BH_3•THF, H_2O_2, NaOH; (c) CrO_3, H_2SO_4; (d) Br_2, KBr; (e) KOH; (f) Amine, recrystallization; (g) MsOH; (h) Br_2, KBr; (i) Bu_3SnH, AIBN; (j) H_2, $Pd(OH)_2/C$, HOAc-THF; (k) BzCl, Py; (l) $Zn(BH_4)_2$,

Fragment 2



Key: (a) NMO, OsO_4, THF-H_2O; (b) BzCl, Py; (c) DMAP; (d) water associate P_{500}; (e) Ac_2O, DMSO, HOAc; (f) KOH, H_2O, MeOH; (g) TBSCl, DMAP, DMF; (h) Cy_2BH, then Et_3NO; (i) $Hg(OAc)_2$, NaCl; (j) I_2, Py

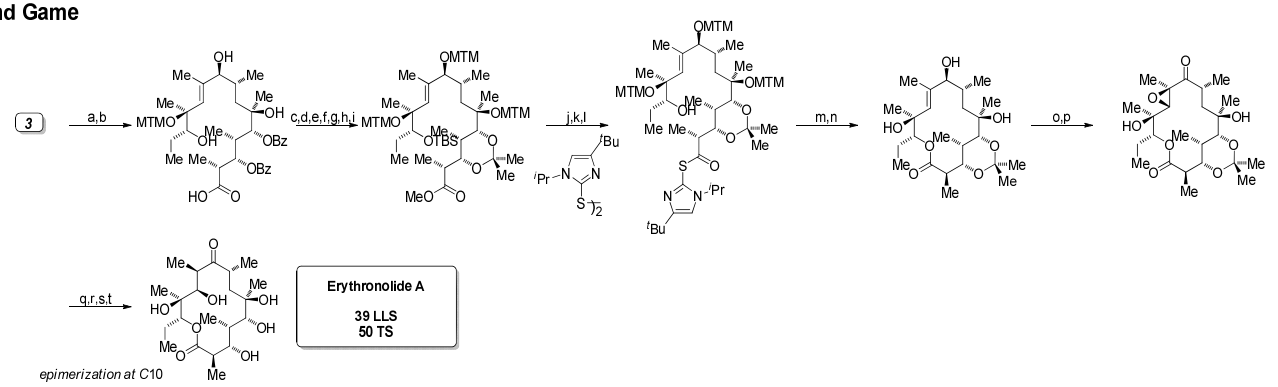
Coupling Fragment 1 and 2



Key: (a) BuLi, $MgBr_2$; (b) $Zn(BH_4)_2$

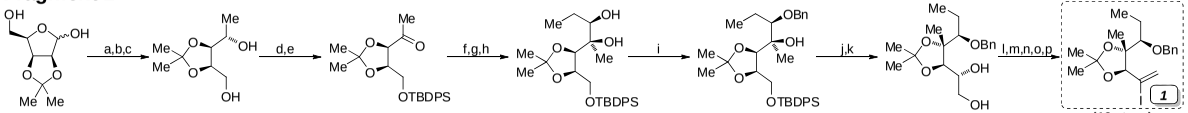
Erythronolide A (Corey, *J. Am. Chem. Soc.* **1979**, *101*, 7131.) (*continued*)

End Game



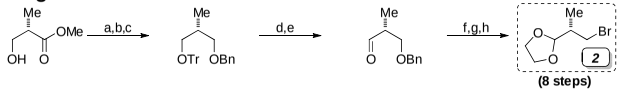
Key: (a) AcOH; (b) LiOH, H_2O_2; (c) KOH; (d) CH_2N_2; (e) $Me_2C(OMe)_2$, Amberlite-50; (f) Ac_2O, DMAP; (g) Ac_2O-DMSO-HOAc; (h) K_2CO_3; (i) Ac_2O-DMSO-HOAc; (j) NaOH, MeOH; (k) TBAF, THF; (l) PPh_3; (m) heating; (n) K_2CO_3, MeI, H_2O, THF; (o) mCPBA; (p) PCC; (q) Pd/C, H_2, (r) CH_2=C(Me)OMe, CSA; (s) Triton B methoxide; (t) PPTS, MeOH

Fragment 1



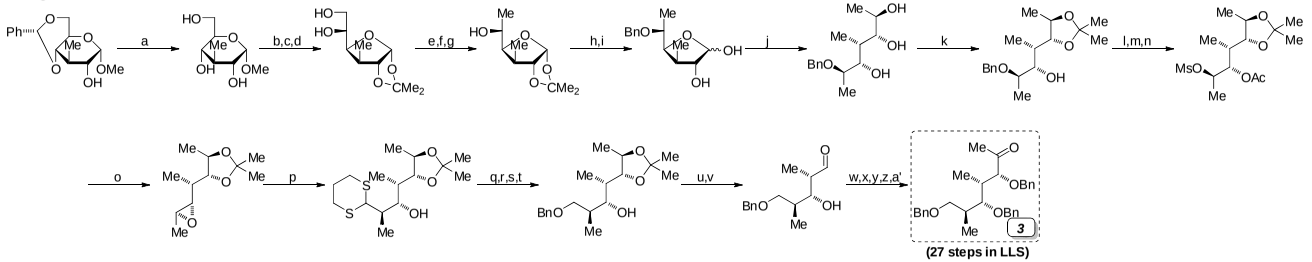
Key: (a) MeMgI; (b) $NaIO_4$; (c) $LiAlH_4$; (d) TBDPSCl, imidazole; (e) PCC; (f) vinylmagnesium bromide; (g) O_3, PPh_3; (h) EtMgBr; (i) NaH, BnBr; (j) $FeCl_3$, acetone; (k) TBAF; (l) $NaIO_4$; (m) MeMgI; (n) PCC; (o) NH_2NH_2-H_2O, TEA; (p) I_2, tetramethylguanidine

Fragment 2



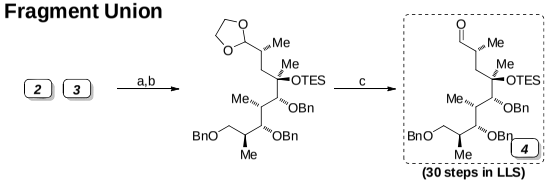
Key: (a) TrCl, TEA, DMAP; (b) LAH; (c) NaH, BnBr; (d) amberlyst^{15}; (e) $(COCl)_2$, TEA, DMSO; (f) $HOCH_2CH_2OH$, TsOH; (g) H_2, Pd/C; (h) EtBr, PPh_3, DEAD

Fragment 3



Key: (a) HCl, MeOH; (b) TsOH, acetone; (c) HCl, H_2O; (d) $FeCl_3$, acetone; (e) TsCl, Py; (f) NaOH; (g) LAH; (h) NaH, BnBr; (i) HCl, H_2O; (j) MeMgBr; (k) $MeC(OMe)_2$, TsOH; (l) Ac_2O, DMAP; (m) H_2, Pd/C; (n) MsCl, Py; (o) LiOH, H_2O; (p) BuLi; (q) Ac_2O, TEA; (r) $HgCl_2$; (s) LAH; (t) NaH, BnBr; (u) HCl, H_2O; (v) $NaIO_4$; (w) $(EtS)_2CH_2$, BuLi; (x) NaH, BnBr; (y) $HgCl_2$; (z) MeMgBr; (a') PCC

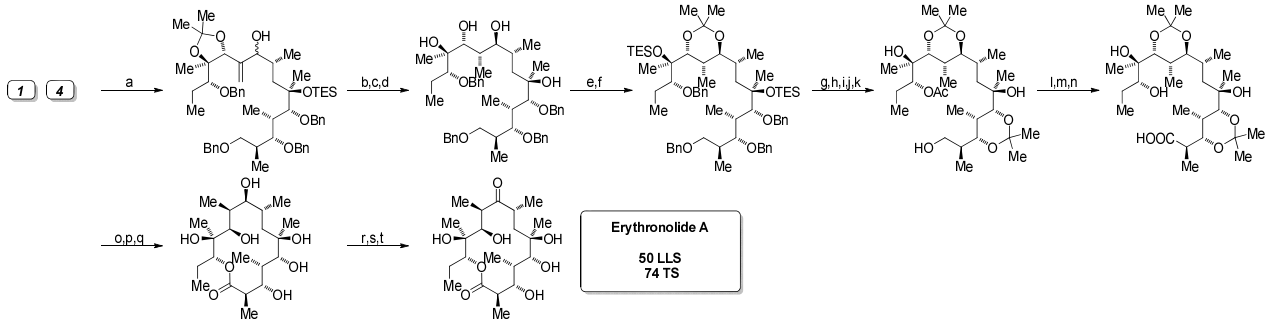
Fragment Union



Key: (a) Mg; (b) TESOTf, 2,6-lutidine; (c) $SnCl_2$, acetone

Erythronolide A (Kinoshita, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2618.) (*continued*)

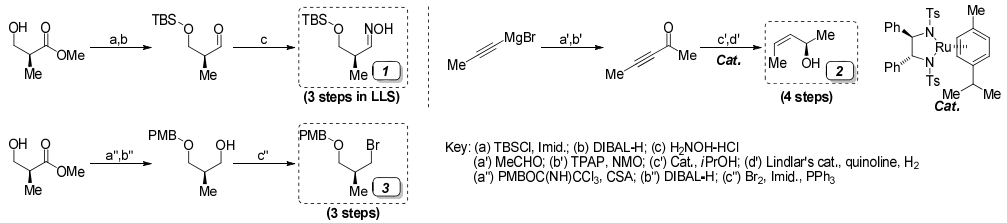
End Game



Key: (a) BuLi; (b) ClRh(PPh$_3$)$_3$, 50 atm H$_2$; (c) TBAF; (d) HCl, H$_2$O; (e) TsOH, acetone; (f) TESOTf, TEA; (g) Pd/C, H$_2$; (h) TBDPSCl, TEA; (i) TsOH, acetone; (j) Ac$_2$O, TEA; (k) TBAF; (l) (COCl)$_2$, TEA, DMSO; (m) NaClO$_2$; (n) LiOH, H$_2$O; (o) (2-pyr)$_2$S$_2$; (p) CuOAc; (q) AcOH; (r) PhCH(OMe)$_2$, CSA; (s) PCC; (t) H$_2$, Pd/C

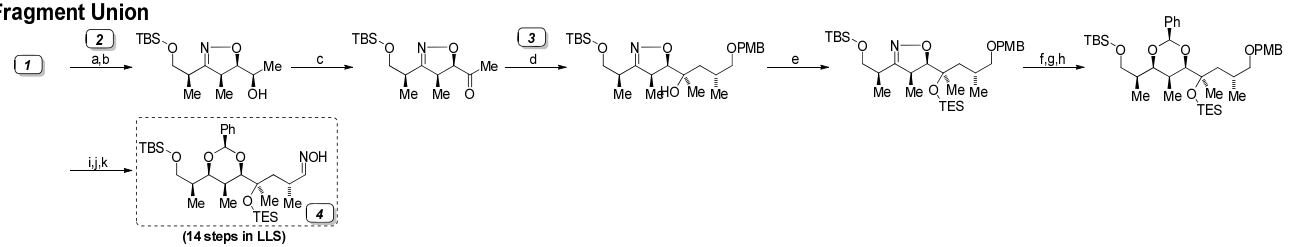
Erythronolide A (Carreira, *Angew. Chem. Int. Ed.* **2005**, *44*, 4036; Carreira, *J. Org. Chem.* **2009**, *74*, 8695.)

Fragment 1, 2, 3



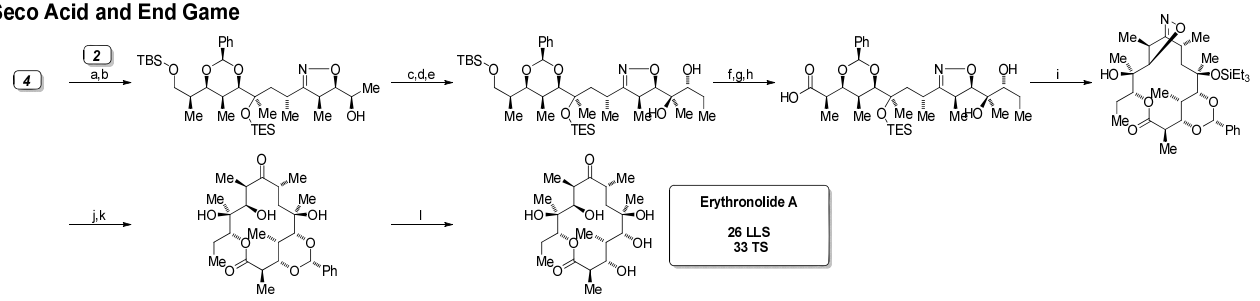
Key: (a) TBSCl, Imid.; (b) DIBAL-H; (c) H_2NOH-HCl
(a') MeCHO; (b') TPAP, NMO; (c') Cat., *i*PrOH; (d') Lindlar's cat., quinoline, H_2
(a'') $PMBOC(NH)CCl_3$, CSA; (b'') DIBAL-H; (c'') Br_2, Imid., PPh_3

Fragment Union



Key: (a) *t*BuOCl; (b) *i*PrOH, ErMgBr; (c) TPAP, NMO; (d) THF; (e) TESOTf, 2,6-lutidine; (f) Raney-Ni, $B(OH)_3$, H_2; (g) $Zn(BH_4)_2$; (h) $PhCH(OMe)_2$, CSA; (i) DDQ; (j) TEMPO, NaOCl; (k) H_2NOH-HCl, Py

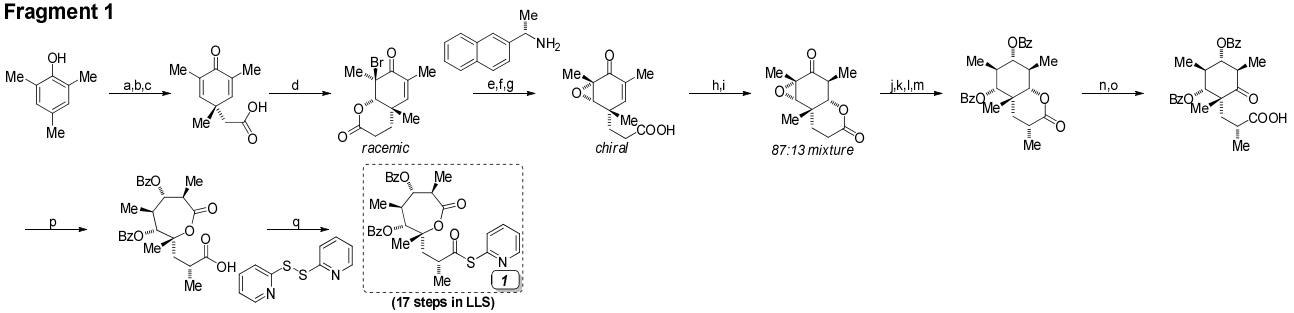
Seco Acid and End Game



Key: (a) *t*BuOCl; (b) *i*PrOH, ErMgBr; (c) TEMPO, NaOCl, KBr; (d) $PrPPh_3Br$, *t*BuLi; (e) $(DHQD)_2PHAL$, $K_3[Fe(CN)_6]$, $MeSO_3NH_2$, K_2CO_3, K_2OsO_4; (f) HF-Py, Py; (g) TEMPO, NaOCl, KBr; (h) $NaClO_2$, 2-methyl-2-butene; (i) 2,4,6-trichlorobenzoyl chloride, TEA, then DMAP; (j) HF-NEt_3, NEt_3; (k) Raney-Ni, AcOH, H_2; (l) $Pd(OAc)_2$, MeOH, H_2

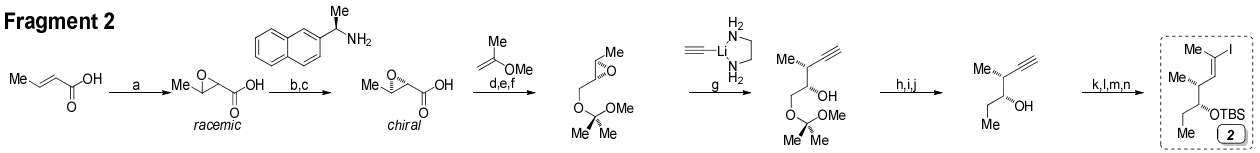
Erythronolide B (Corey, *J. Am. Chem. Soc.* **1978**, *100*, 5620.)

Fragment 1



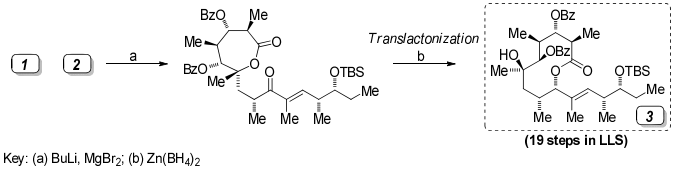
Key: (a) Allyl-Br, NaOMe; (b) BH_3•THF, H_2O_2, NaOH; (c) CrO_3, H_2SO_4; (d) Br_2, KBr; (e) KOH; (f) Amine, recrystallization; (g) MsOH; (h) Br_2, KBr; (i) Bu_3SnH, AIBN; (j) Al/Hg; (k) H_2, Raney-Ni; (l) BzCl, Py; (m) MeI, LDA, HMPA; (n) LiOH; (o) CrO_3, H_2SO_4; (p) AcOOH; (q) PPh_3

Fragment 2



Key: (a) H_2O_2, Na_2WO_4; (b) Amine, recrystallization; (c) MsOH; (d) $ClCO_2Et$, TEA; (e) $NaBH_4$; (f) $POCl_3$; (g) Lithium reagent; (h) Amberlite-50; (i) MsCl, Py; (j) Me_2CuLi; (k) TBSCl, Imidazole; (l) LDA, MeI; (m) Cp_2ZrHCl; (n) I_2, CCl_4

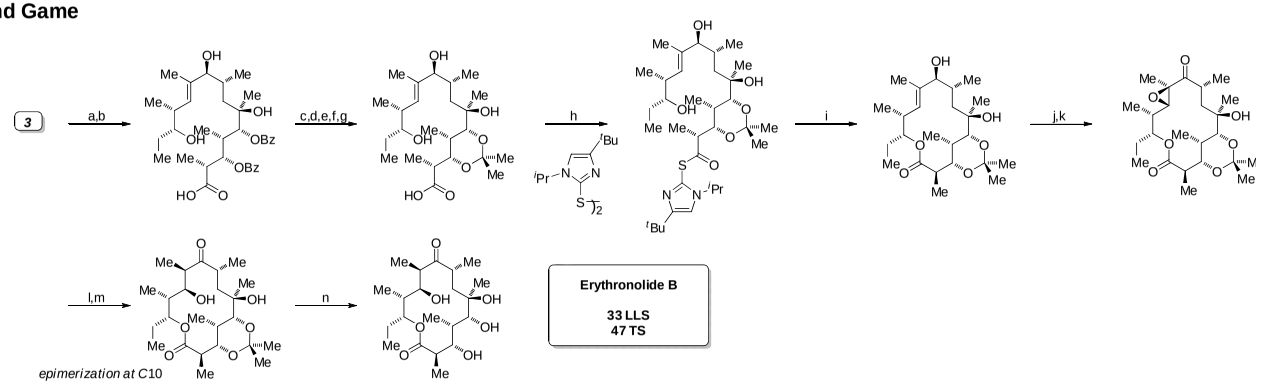
Coupling Fragment 1 and 2



Key: (a) BuLi, $MgBr_2$; (b) $Zn(BH_4)_2$

Erythronolide B (Corey, *J. Am. Chem. Soc.* **1978**, *100*, 5620.) (*continued*)

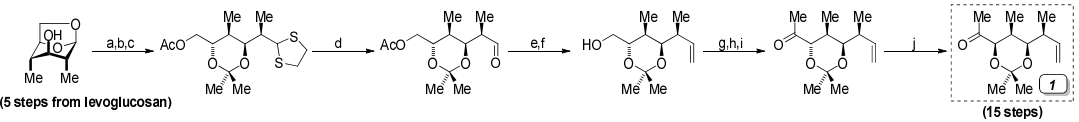
End Game



Key: (a) AcOH; (b) LiOH, H_2O_2; (c) KOH; (d) CH_2N_2; (e) HBr; (f) $Me_2C(OMe)_2$, Amberlite-50; (g) KOH; (h) PPh_3; (i) Heating; (j) MnO_2; (k) H_2O_2, NaOH; (l) H_2, Pd/C; (m) K_2CO_3; (n) HCl

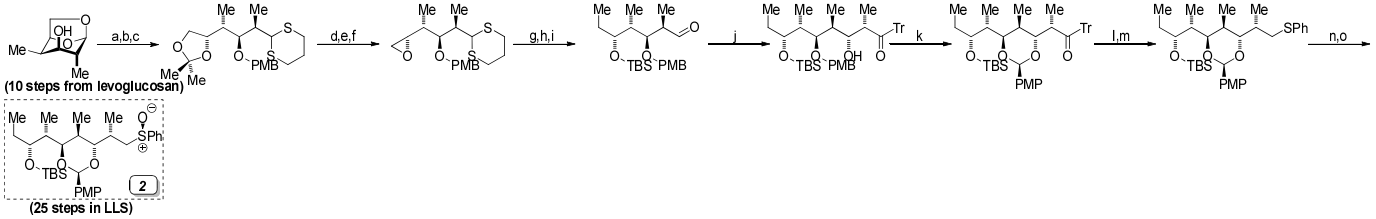
Erythronolide B (Kochetkov, *Tetrahedron Lett.* **1987**, *28*, 3835.)

Fragment 1



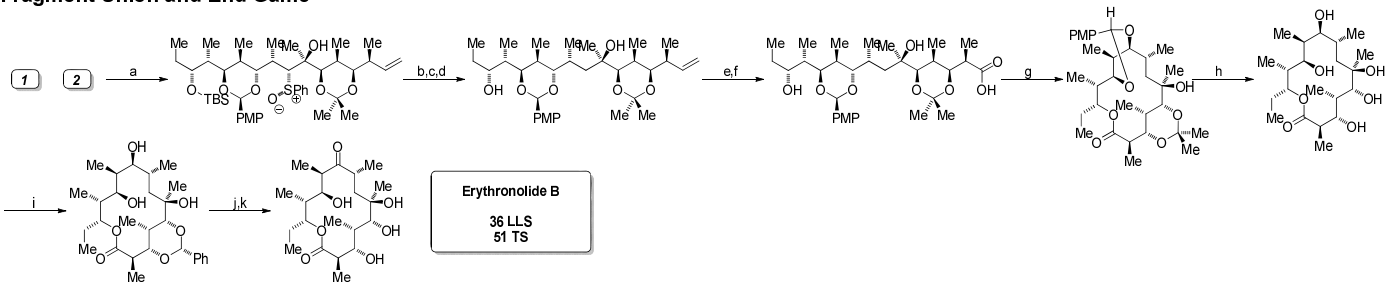
Key: (a) $HS(CH_2)_2SH$, BF_3OEt_2; (b) Ac_2O-Py; (c) DMP-Me_2CO, TsOH; (d) $HgCl_2$, $CaCO_3$; (e) $Ph_3P{=}CH_2$; (f) MeONa, MeOH; (g) $(COCl)_2$, DMSO, TEA; (h) MeMgCl; (i) $(COCl)_2$, DMSO, TEA; (j) K_2CO_3, MeOH

Fragment 2



Key: (a) $HS(CH_2)_2SH$, BF_3OEt_2; (b) DMP-Me_2CO, TsOH; (c) NaH, PMBCl; (d) AcOH, H_2O; (e) TsCl, Py; (f) K_2CO_3, MeOH; (g) MeMgCl, CuCl-Me_2S, THF; (h) *t*-$BuPh_2SiClO_4$, TEA; (i) $HgCl_2$-$CdCO_3$; (j) C_2H_5COTr, BuLi; (k) DDQ, 3A MS, DCM; (l) $LiBHEt_3$; (m) Ph_2S_2, PBu_3, Py; (n) MCPBA, FAA; (o) collidine

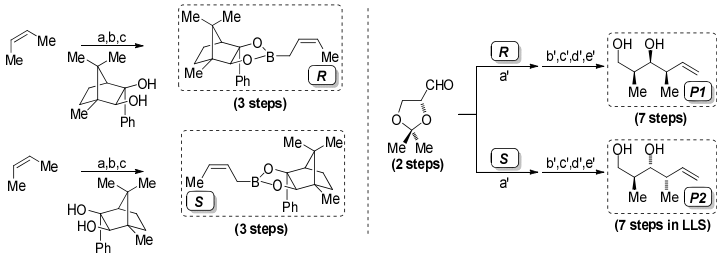
Fragment Union and End Game



Key: (a) LDA, THF; (b) TFAA, NaI, Me_2CO; (c) Na, NH_3; (d) TBAF, THF; (e) O_3; (f) mCPBA, pH = 7 buffer; (g) 2,2'-dithiobis(4-t-bu-t-i-pr-imidazole), PPh_3, $PhCH_3$; (h) TFA; (i) $PhCH(OEt)_2$, CSA; (j) PCC, 3A MS; (k) AcOH, H_2O

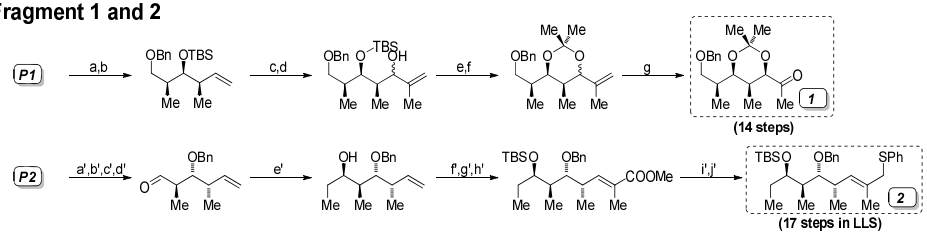
Erythronolide B (Mulzer, *J. Am. Chem. Soc.* **1991**, *113*, 910.)

Chiral Auxiliary and Precursor 1,2



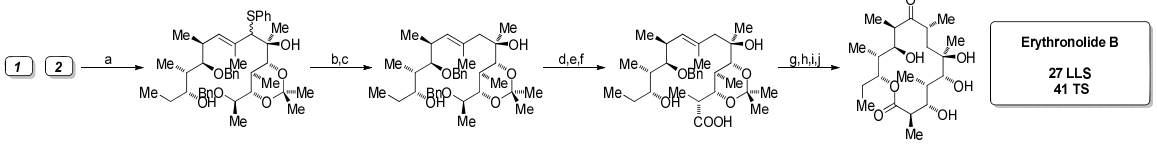
Key: (a) BuLi, *t*BuOK; (b) Cl-B(NMe$_2$)$_2$; (c) distillation
(a') -78 ºC; (b') TsCl; (c') PPTS; (d') NaHCO$_3$; (e') Me$_2$CuLi

Fragment 1 and 2



Key: (a) NaH, BnBr; (b) TBSCl, Imid.; (c) O$_3$, PPh$_3$; (d) H$_2$C=C(Me)-MgBr; (e) TBAF; (f) DMP, H$^+$; (g) O$_3$, PPh$_3$
(a') TrCl, DMAP, Py; (b') NaH, BnBr; (c') HCOOH, then KOH; (d') (COCl)$_2$, DMSO, TEA; (e') EtMgBr; (f') TBSCl, TEA; (g') O$_3$, PPh$_3$; (h') Ph$_3$P-C(Me)COOMe; (i') DIBAL-H; (j') Bu$_3$P, (PhS)$_2$, Py

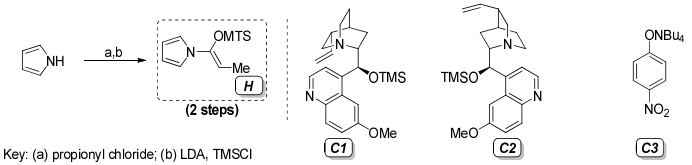
Fragment Union and End Game



Key: (a) BuLi, TMEDA, then BF$_3$; (b) Li/EtNH$_2$; (c) Ac$_2$O, DMAP, Py; (d) *t*BuOK; (e) PDC, DMF; (f) NaOH; (g) 2,4,6-trichlorobenzoyl chloride, TEA, then DMAP; (h) BH$_3$•SMe$_2$, then H$_2$O$_2$; (i) PCC; (j) 80% HOAc

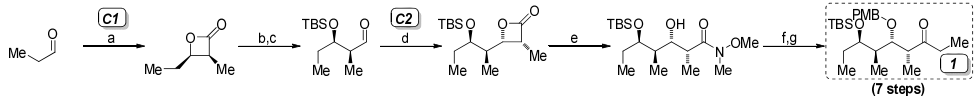
Erythronolide B (Nelson, *Angew. Chem. Int. Ed.* **2010**, *49*, 2591.)

Catalyst and Homologation Reagent



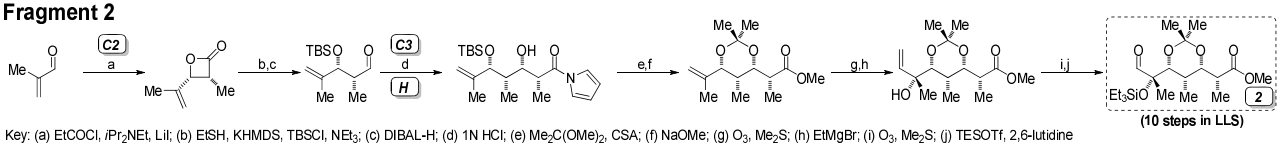
Key: (a) propionyl chloride; (b) LDA, TMSCl

Fragment 1



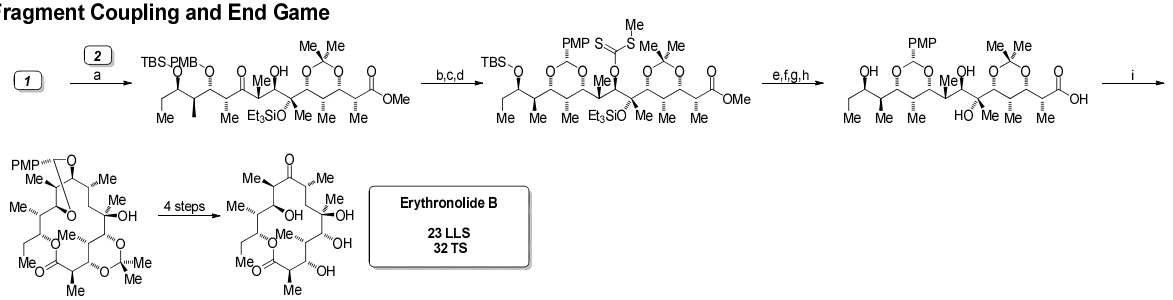
Key: (a) EtCOCl, iPr$_2$NEt, LiClO$_4$; (b) EtSH, KHMDS; (c) DIBAL•H; (d) EtCOCl, iPr$_2$NEt, LiI; (e) MeO(Me)NH$_2$Cl, Me$_2$AlCl; (f) EtMgBr; (g) PMBOC(NH)CCl$_3$, BF$_3$•OEt$_2$

Fragment 2



Key: (a) EtCOCl, iPr$_2$NEt, LiI; (b) EtSH, KHMDS, TBSCl, NEt$_3$; (c) DIBAL-H; (d) 1N HCl; (e) Me$_2$C(OMe)$_2$, CSA; (f) NaOMe; (g) O$_3$, Me$_2$S; (h) EtMgBr; (i) O$_3$, Me$_2$S; (j) TESOTf, 2,6-lutidine

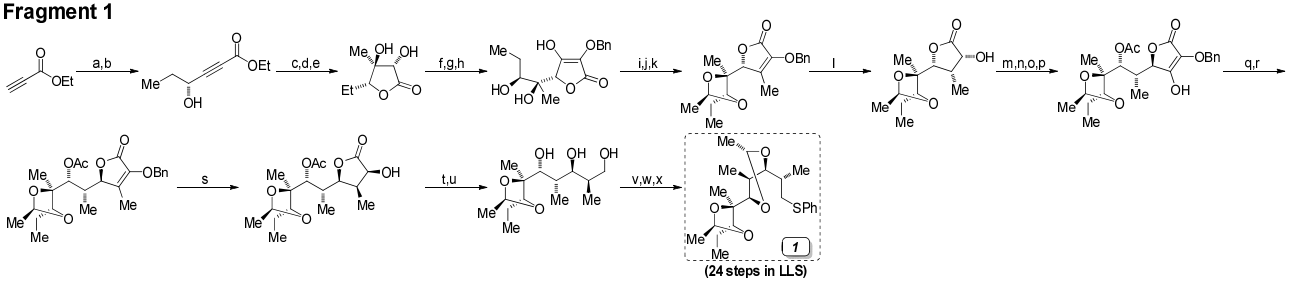
Fragment Coupling and End Game



Key: (a) LHMDS; (b) Zn(BH$_4$)$_2$; (c) DDQ; (d) KHMDS, CS$_2$, MeI; (e) AIBN, Bu$_3$SnH; (f) PMPCH(OMe)$_2$, CSA; (g) LiOH; (h) TBAF; (i) 2,4,6-trichlorobenzoyl chloride, TEA, then DMAP

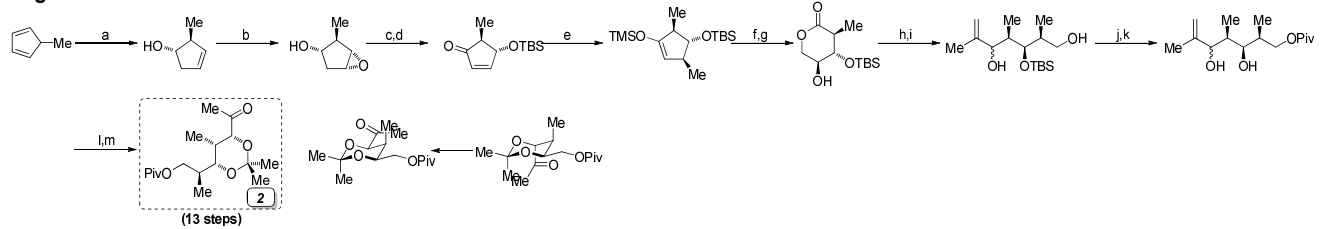
(9S)-Dihydroerythronolide A (Stork, *J. Am. Chem. Soc.* **1987**, *109*, 1565.)

Fragment 1



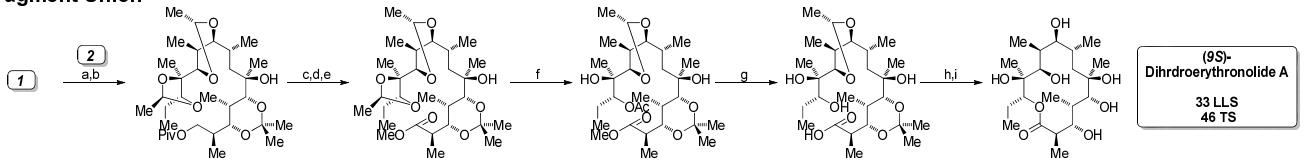
Key: (a) BuLi, propionyl chloride; (b) 9-BBN, (*R*)-pinene; (c) H_2C=C(Me)OMe, CSA; (d) dimethylthiocuprate, then acid; (e) OsO_4, NMO; (f) TMSCl, Imid.; (g) LHMDS, $EtOC(O)CH_2OBn$; (h) K_2CO_3; (i) $MeCH(COMe)_2$, CSA; (j) $(PhO)_2P(O)Cl$, Na_2CO_3, TBABr; (k) Me_2Zn, $Ni(acac)_2$; (l) H_2, Pd/C; (m) $TMSNMe_2$; (n) LHMDS, $EtOC(O)CH_2OBn$; (o) K_2CO_3; (p) Ac_2O, TEA, DMAP; (q) $(PhO)_2P(O)Cl$, Na_2CO_3, TBABr; (r) Me_2Zn, $Ni(acac)_2$; (s) Rh/Alumina, H_2; (t) LAH, HOAc, HIO_4; (u) $NaBH_4$; (v) $CH_3C(OEt)_3$, PPTS; (w) BH_3-THF; (x) $(PhS)_2$, PPh_3

Fragment 2



Key: (a) (*R*)-pinene, BH_3-THF, then H_2O_2; (b) $VO(acac)_2$; (c) CrO_3, H_2SO_4; (d) NEt_3, then TBSCl, DMAP; (e) $LiCuMe_2$, then TMSCl; (f) O_3, $NaBH_4$; (g) 2N HCl; (h) DIBAL-H; (i) 2-propenyl lithium; (j) TBAF; (k) PivCl, DMAP, TEA; (l) $Me_2C(OMe)_2$, PPTS; (m) O_3, PPh_3

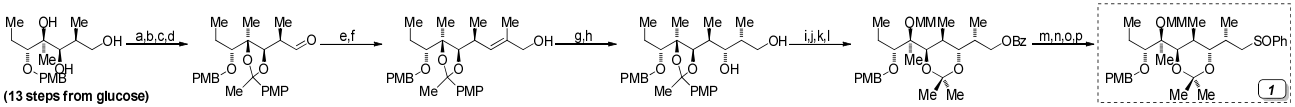
Fragment Union



Key: (a) 4,4'-dibutylbiphenyl, Li; (b) $MgBr_2$; (c) MeLi; (d) PDC; (e) Me_2SO_4; (f) O_3; (g) KOH, aq. MeOH; (h) DCC, DMAP, refluxing chloroform; (i) HCl

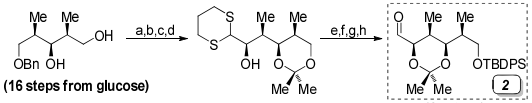
(9*S*)-Dihydroerythronolide A (Yonemitsu, *Tetrahedron Lett.* **1987**, *28*, 4569.)

Fragment 1



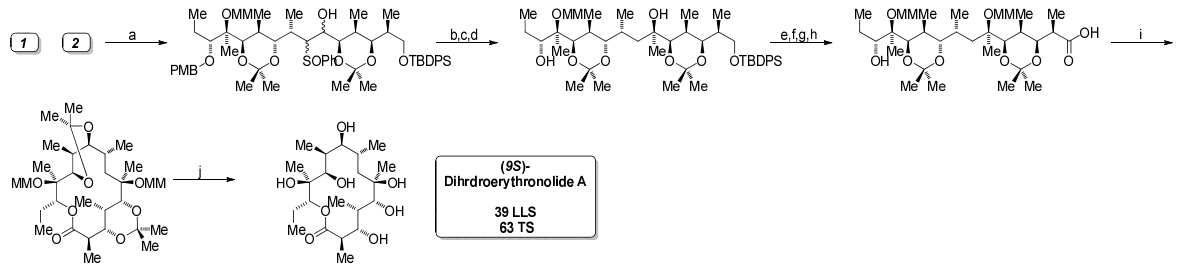
Key: (a) BzCl, Py; (b) $PMPCMe(OMe)_2$, CSA; (c) 1N KOH, MeOH; (d) $(COCl)_2$, DMSO, TEA; (e) $Ph_3P{=}CMeCO_2Et$, EDC; (f) LAH; (g) mCPBA; (h) $NaBH_3CN$, BF_3OEt_2; (i) BzCl, Py; (j) 4N HCl; (k) $CH_2{=}C(Me)OMe$, PPTS; (l) MMCl, *i*-Pr_2NEt; (m) 1N NaOH; (n) TsCl, TEA, DMAP; (o) PhSNa, EtOH; (p) $NaIO_4$

Fragment 2



Key: (a) $Me_2C(OMe)_2$, CSA; (b) 10% Pd-C, H_2; (c) PCC, 4A MS; (d) $HS(CH_2)_3SH$, BuLi; (e) TsOH; (f) TBDPSCl, imid.; (g) $CH_2{=}C(Me)OMe$, PPTS; (h) MeI, $NaHCO_3$

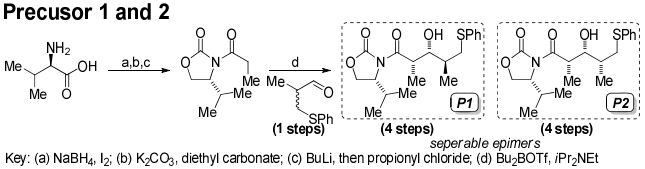
Fragment Union and Macrocyclization



Key: (a) LDA; (b) Raney Ni; (c) $(COCl)_2$, DMSO, TEA; (d) MeLi; (e) MMCl, *i*-Pr_2NEt; (f) TBAF; (g) Jones reagent; (h) 10% Pd/C, H_2; (i) 2,4,6-$Cl_3C_6H_2COCl$, TEA, then DMAP; (j) 50% HOAc

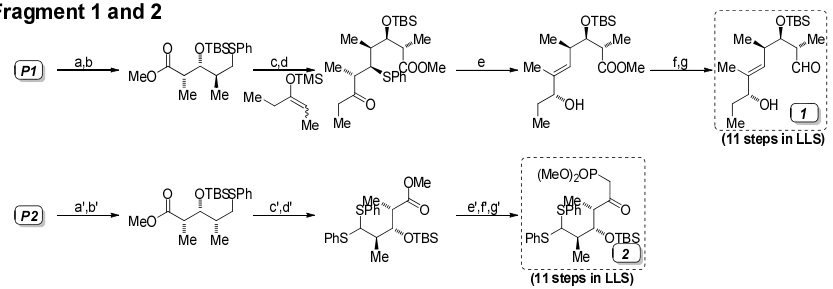
(9S)-Dihydroerythronolide A (Paterson, *Tetrahedron Lett.* **1989**, *30*, 7463.)

Precusor 1 and 2



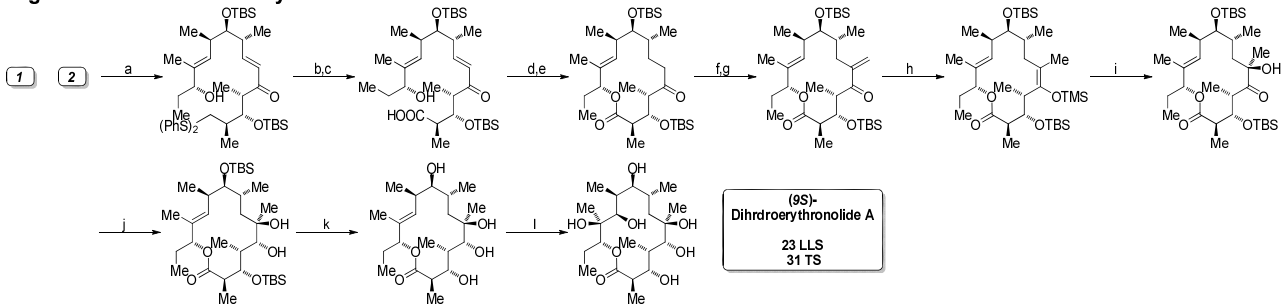
Key: (a) $NaBH_4$, I_2; (b) K_2CO_3, diethyl carbonate; (c) BuLi, then propionyl chloride; (d) Bu_2BOTf, iPr_2NEt

Fragment 1 and 2



Key: (a) NaOMe; (b) TBSOTf, 2,6-lutidine; (c) NCS; (d) $ZnBr_2$; (e) $NaIO_4$; (f) (+)-*N*-methylephedrine, *N*-ethylaniline, LAH; (g) DIBAL-H
(a') NaOMe; (b') TBSOTf, 2,6-lutidine; (c') NCS; (d') $PhSSiMe_3$, $ZnBr_2$; (e') BuLi; (f') (+)-*N*-methylephedrine, *N*-ethylaniline, LAH; (g') DIBAL-H

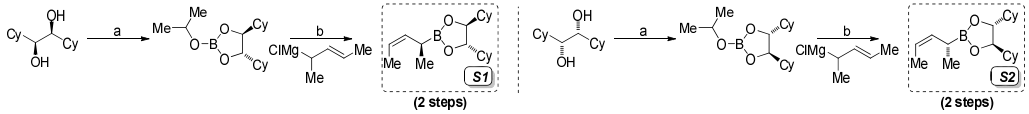
Fragment Union and Macrocyclization



Key: (a) iPr_2NEt, LiCl; (b) HgO, *aq.* HBF_4; (c) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4; (d) 2,4,6-trichlorobenzoyl chloride, TEA, then DMAP; (e) H_2, Rh/Al_2O_3; (f) LDA, CH_2O; (g) MsCl, TEA, then DBU; (h) L-selectride, then TMSCl; (i) OsO_4, NMO, quinuclidine; (j) $Zn(BH_4)_2$; (k) 40% *aq.* HF; (l) OsO_4, NMO, then $Na_2S_2O_5$

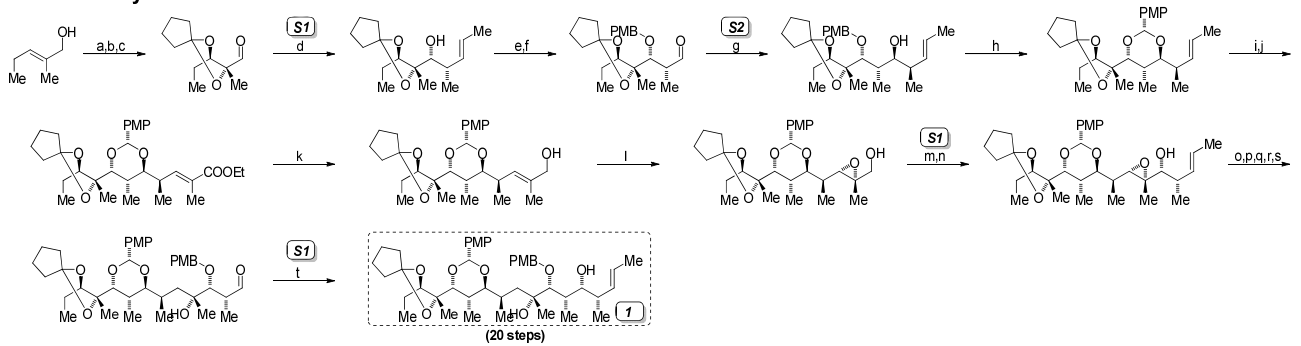
(9*S*)-Dihydroerythronolide A (Hoffmann, *Angew. Chem. Int. Ed.* **1993**, *32*, 101.)

Chiral Auxiliary



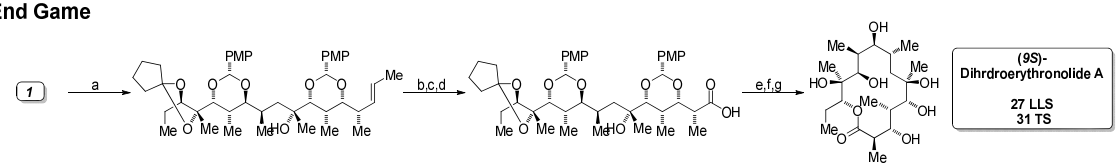
Key: (a) *i*PrOH; (b) THF, 0°C

Iterative Crotylation



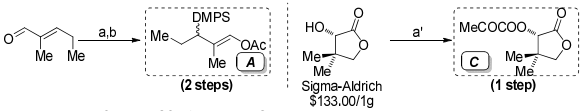
Key: (a) (+)-dimethyl tartrate, $Ti(O/Pr)_4$, tBu_2O_2; (b) $(COCl)_2$, TEA, DMSO; (c) $SnCl_4$, cyclopentanone; (d) 3d, benzene, 80°C; (e) NaH, PMBCl; (f) O_3, PPh_3; (g) pet. ether, 2d; (h) DDQ; (i) O_3, PPh_3; (j) $Ph_3PCH(CH_3)COOEt$; (k) LAH; (l) *t*BuOOH, (+)-dimethyl tartrate, $Ti(O/Pr)_4$; (m) NMO, TPAP; (n) 10 kbar, pet. ether, 3d; (o) *i*PrMgCl; (p) LAH; (q) PMBCl, NaH; (r) NMO, OsO_4; (s) $NaIO_4$; (t) 10 kbar, pet. ether, 3d

End Game



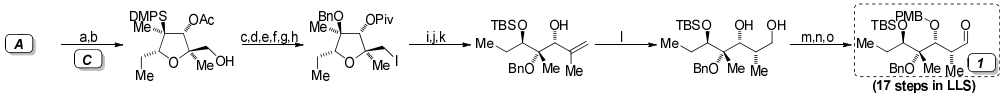
Key: (a) DDQ; (b) NMO, OsO_4; (c) $NaIO_4$; (d) CrO_3, acetone; (e) TNT, 2N HCl; (f) 2,4,6-trichlorobenzoyl chloride, TEA, then DMAP; (g) 2N HCl

Allylsilane and Auxillary Synthesis



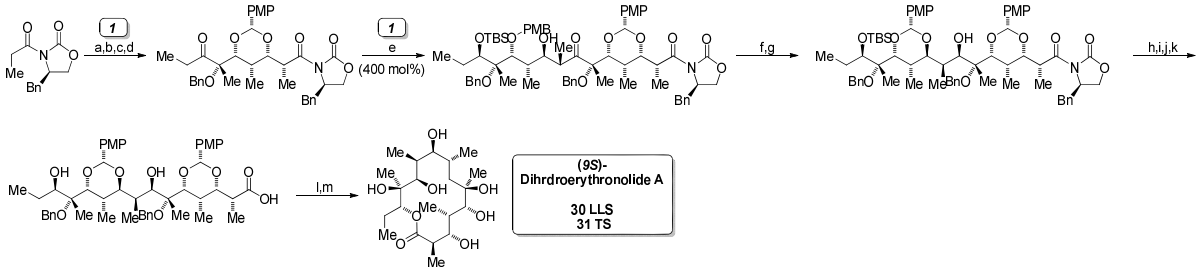
Key: (a) Li, then CuI, DMPSCl; (b) BuLi, Ac_2O
(a') MeCOCOCl, NEt_3, DMAP

Common Precursor 1



Key: (a) $TiCl_4$; (b) LAH; (c) NaH, PMBCl; (d) $PhMe_2CCOOH$; (e) NaH, BnBr; (f) CAN; (g) I_2, PPh_3; (h) Piv_2O, $Sc(OTf)_3$; (i) Zn, HOAc; (j) TBSOTf; (k) DIBAL•H; (l) HMDS, Pt(0), H_2O_2; (m) $MeOC_6H_4CH(OMe)_2$, PPTS; (n) DIBAL•H; (o) $(COCl)_2$, DMSO, TEA

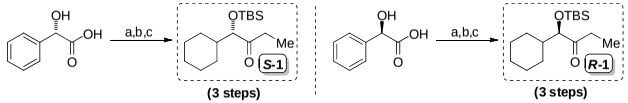
Fragment Union



Key: (a) $TiCl_4$, (-)-sparteine; (b) DDQ; (c) HF-Py, Py; (d) $(COCl)_2$, DMSO, TEA; (e) $Sn(OTf)_2$, TEA; (f) $Zn(BH_4)_2$; (g) DDQ; (h) NaH, CS_2, MeI; (i) AIBN, Bu_3SnH; (j) LiOOH; (k) TBAF; (l) 2,4,6-trichlorobenzoyl chloride, TEA, then DMAP; (m) H_2, $Pd(OH)_2/C$

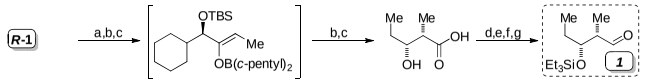
6-Deoxyerythronolide B (Masamune, *J. Am. Chem. Soc.* **1981**, *103*, 1568.)

Auxiliary Preparation



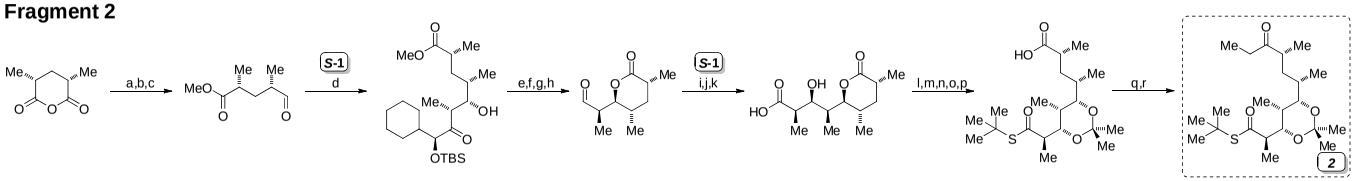
Key: (a) Rh/Al_2O_3; (b) EtLi, -78 °C; (c) TBSOTf, 2,6-lutidine

Fragment 1



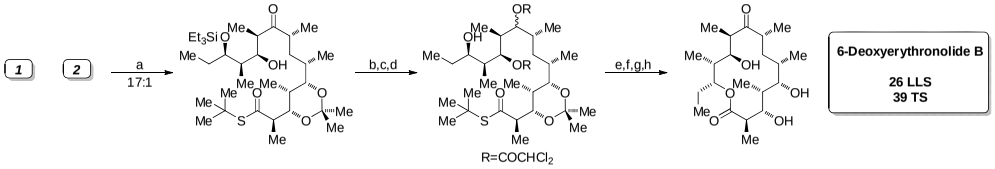
Key: (a) *c*-pentylBOTf, iPr_2NEt, then acetyl aldehyde; (b) HF-MeCN; (c) $NaIO_4$; (d) CH_2N_2; (e) TESCl, DMAP; (f) DIBAL-H; (g) CrO_3•2Py

Fragment 2



Key: (a) lipase, MeOH; (b) $(COCl)_2$; (c) Pd-$BaSO_4$, H_2; (d) ***S*-1**, *c*-pentylBOTf, iPr_2NEt; (e) HF-MeCN; (f) $NaIO_4$; (g) $(COCl)_2$; (h) Pd-$BaSO_4$, H_2; (i) ***S*-1**, *c*-pentylBOTf, iPr_2NEt; (j) TBAF; (k) $NaIO_4$; (l) $ClCO_2Et$, Py; (m) TlS*t*Bu, HS*t*Bu; (n) KOH, H_2O; (o) TBDPSCl, DMF; (p) $MeC(OMe)=CH_2$, TFA; (q) $(COCl)_2$, Py; (r) $LiCuEt_2$

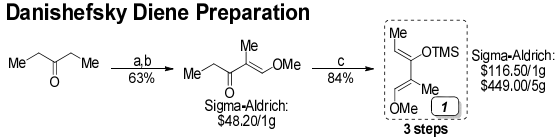
End Game



Key: (a) LHMDS; (b) $NaBH_4$, MeOH; (c) $(CHCl_2CO)_2O$, Py; (d) HOAc; (e) CuOTf, iPr_2NEt; (f) KOH, H_2O/THF/MeOH; (g) PCC; (h) TFA, $MeCN/H_2O$

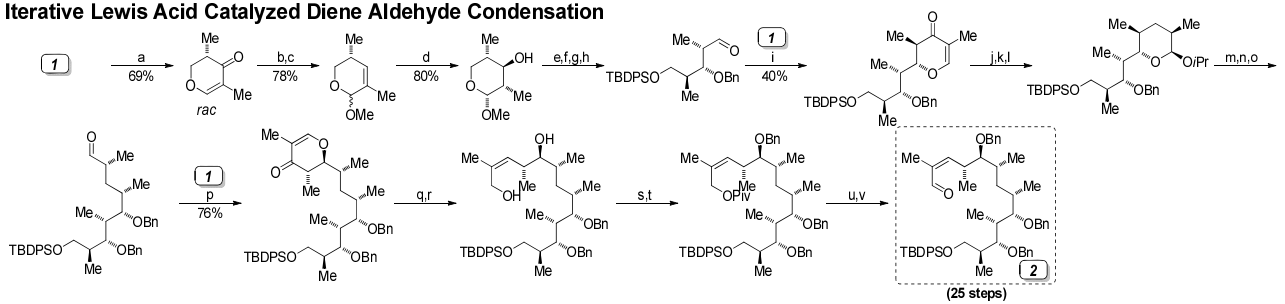
6-Deoxyerythronolide B (Danishefsky, *J. Org. Chem.* **1990**, *55*, 1636.)

Danishefsky Diene Preparation



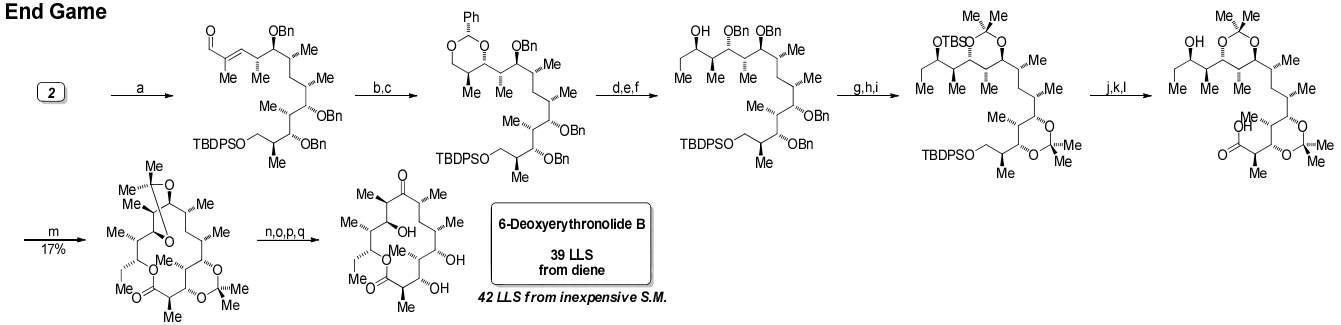
Key: (a) NaH, then ethyl formate; (b) TsOH, relux; (c) TMSOTf, TEA

Iterative Lewis Acid Catalyzed Diene Aldehyde Condensation



Key: (a) $ZnCl_2$, formaldehyde; (b) $CeCl_3$, $NaBH_4$; (c) TsOH; (d) BH_3•SMe_2; (e) 1,3-propanedithiol, $TiCl_4$; (f) TBDPSCl, TEA; (g) NaH, BnBr, TBAI; (h) NBS, $NaHCO_3$; (i) $ZnCl_2$, BF_3•OEt_2; (j) $CeCl_3$, $NaBH_4$; (k) TsOH, *i*PrOH; (l) Pd/Al_2O_3, H_2 (50 psi); (m) 1,3-propanedithiol, $TiCl_4$; (n) NaH, BnBr, TBAI; (o) NBS, acetone; (p) $ZnCl_2$, BF_3•OEt_2; (q) $CeCl_3$, $NaBH_4$; (r) TsOH, then $LiBH_4$; (s) PivCl, TEA; (t) $BnC(NH)CCl_3$, TfOH; (u) LAH; (v) Dess-Martin periodate

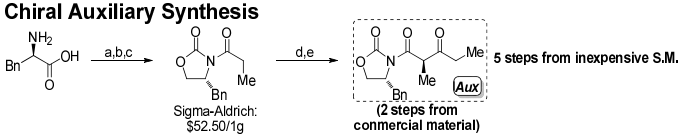
End Game



Key: (a) PhSH, BuLi; (b) BH_3•SMe_2; (c) $PhCH(OMe)_2$, PPTS; (d) DIBAL-H; (e) Dess-Martin periodate; (f) EtMgBr; (g) TBSOTf, TEA; (h) Li/NH_3 (i) $(MeO)_2CH_2$, CSA; (j) TBAF, reflux; (k) $RuCl_2(PPh_3)_3$; (l) 2-methyl-2-butene, NaH_2PO_4, $NaClO_2$; (m) TEA, 2,4,6-trichlorobenzoyl chloride, then DMAP; (n) CSA; (o) $(MeO)_2CH_2$, CSA; (p) PCC; (q) TFA, $MeCN/H_2O$

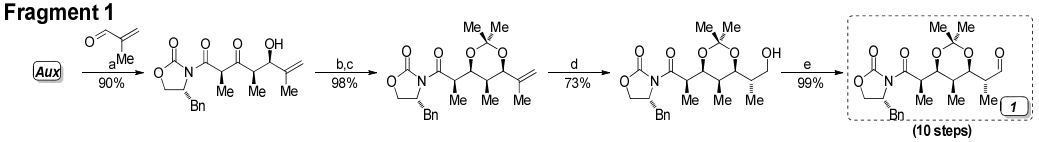
6-Deoxyerythronolide B (Evans, *Tetrahedron Lett.* **1997**, *38*, 53; *J. Am. Chem. Soc.* **1998**, *120*, 5921.)

Chiral Auxiliary Synthesis



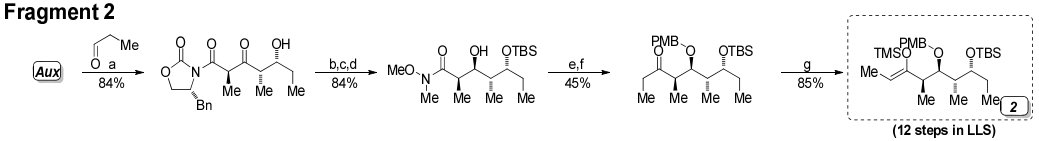
Key: (a) $NaBH_4$, I_2; (b) K_2CO_3, diethyl carbonate; (c) BuLi, then propionyl chloride; (d) Cy_2BOTf, iPr_2NEt, then propionaldehyde; (e) SO_3•Py, TEA, DMSO

Fragment 1



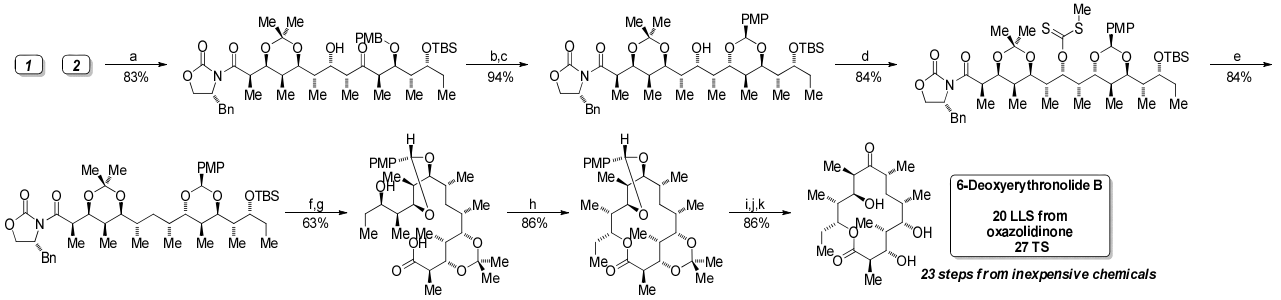
Key: (a) $TiCl_4$, iPr_2NEt, then methacrolein; (b) $Zn(BH_4)_2$; (c) $Me_2C(OMe)_2$, CSA; (d) 9-BBN; (e) $(COCl)_2$, TEA, DMSO

Fragment 2



Key: (a) $Sn(OTf)_2$, TEA, then propionaldehyde; (b) $NaBH(OAc)_3$, AcOH; (c) TBSOTf, 2,6-lutidine; (d) $AlMe_3$, (MeO)MeNH•HCl; (e) EtMgBr; (f) $Cl_3CC(NH)O$-(*p*-OMe)Bn, TfOH; (g) BuLi, $(PhMe_2Si)_2NH$, TMSOTf, 2,6-lutidine

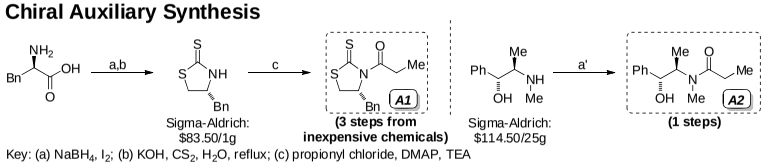
End Game



Key: (a) BF_3•OEt_2; (b) $Zn(BH_4)_2$; (c) DDQ; (d) NaH, then CS_2, then MeI; (e) AIBN, Bu_3SnH; (f) LiOOH; (g) TBAF; (h) TEA, 2,4,6-trichlorobenzoyl chloride, then DMAP (i) $Pd(OH)_2$/C, *i*PrOH; (j) PCC; (k) 1M HCl

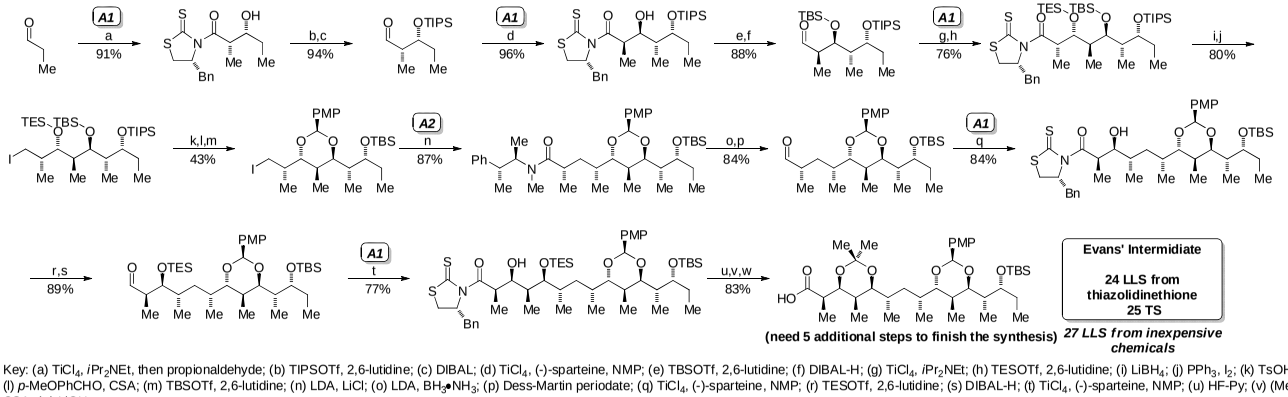
6-Deoxyerythronolide B (Crimmins, *Org. Lett.* **2006**, *8*, 2191.)

Chiral Auxiliary Synthesis



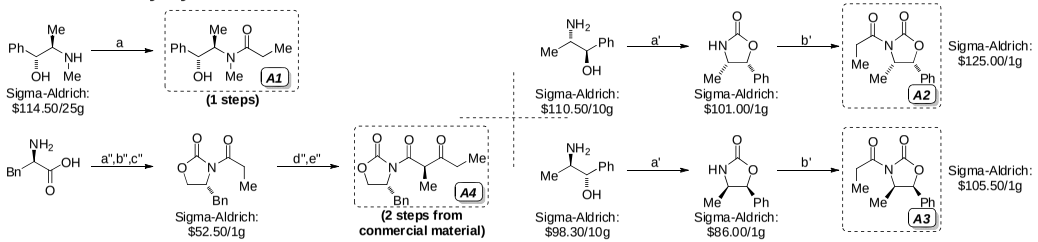
Key: (a) $NaBH_4$, I_2; (b) KOH, CS_2, H_2O, reflux; (c) propionyl chloride, DMAP, TEA

Iterative Aldol Addition



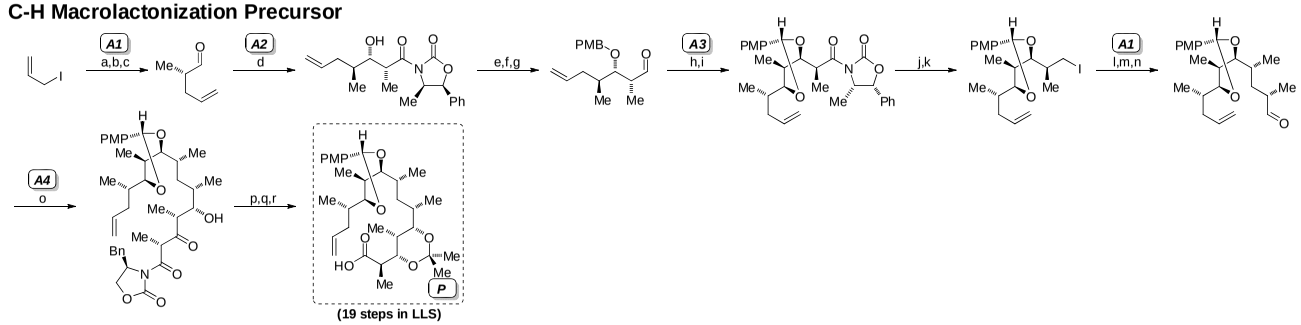
Key: (a) $TiCl_4$, iPr_2NEt, then propionaldehyde; (b) TIPSOTf, 2,6-lutidine; (c) DIBAL; (d) $TiCl_4$, (-)-sparteine, NMP; (e) TBSOTf, 2,6-lutidine; (f) DIBAL-H; (g) $TiCl_4$, iPr_2NEt; (h) TESOTf, 2,6-lutidine; (i) $LiBH_4$; (j) PPh_3, I_2; (k) TsOH, MeOH; (l) *p*-MeOPhCHO, CSA; (m) TBSOTf, 2,6-lutidine; (n) LDA, LiCl; (o) LDA, BH_3•NH_3; (p) Dess-Martin periodate; (q) $TiCl_4$, (-)-sparteine, NMP; (r) TESOTf, 2,6-lutidine; (s) DIBAL-H; (t) $TiCl_4$, (-)-sparteine, NMP; (u) HF-Py; (v) $(MeO)_2CMe_2$, CSA; (w) LiOH

Chiral Auxiliary Synthesis



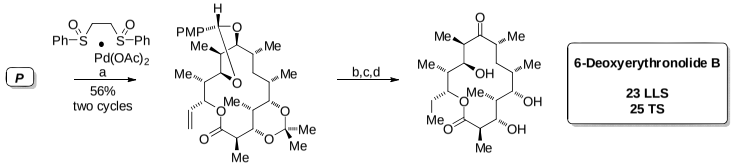
Key: (a) propionyl chloride, DMAP, TEA; (a') K_2CO_3, diethyl carbonate; (b') BuLi, then propionyl chloride; (a") $NaBH_4$, I_2; (b") K_2CO_3, diethyl carbonate; (c") BuLi, then propionyl chloride; (d") Cy_2BOTf, iPr_2NEt, then propionaldehyde; (e") SO_3·Py, TEA, DMSO

C-H Macrolactonization Precursor



Key: (a) LDA, LiCl; (b) LDA, BH_3•NH_3; (c) $(COCl)_2$, DMSO, TEA; (d) Bu_2BOTf, iPr_2NEt; (e) $AlMe_3$, (MeO)NHMe•HCl; (f) PMBBr, NaH; (g) DIBAL-H; (h) Bu_2BOTf, TEA; (i) DDQ; (j) LAH; (k) PPh_3, I_2, imidazole; (l) LDA, LiCl; (m) TBSOTf, 2,6-lutidine; (n) LDA, LiCl; (o) $Ti(OiPr)Cl_3$, TEA; (p) $Zn(BH_4)_2$; (q) $(MeO)_2CMe_2$, CSA; (r) LiOOH

End Game: C-H Macrolactonization

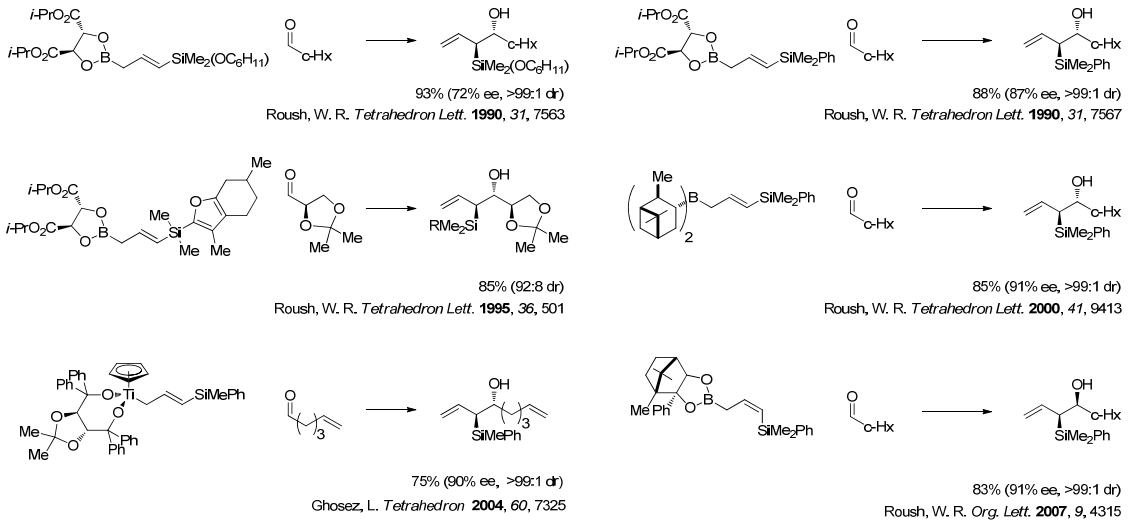


Key: (a) Cat., benzoquinone; (b) $Pd(OH)_2$/C, H_2; (c) TPAP, NMO; (d) 1M HCl

CHAPTER 2: TRANSITION METAL CATALYZED *ANTI*-DIASTEREO- AND ENANTIOSELECTIVE CARBONYL SILYLALLYLATION[1]

2.1 INTRODUCTION

Carbonly silylallylation reaction has been attracted for many years because the product is a very important synthetic intermediate in organic reaction (Scheme 2.1).[2] For example, Roush utilized (E)-γ-(alkoxysilyl)allyl boronate for the construction of diol. Since then, various reagents have been developed from the same group to increase the selectivity. Recently, chiral silyl allyl Titinium reagent was used to give β-hydroxyallylsilanes with high reactivity and selectivity. These types of reagents share common drawbacks such as generating stoichiometric amount of byproducts and requiring multiple steps for preparation.

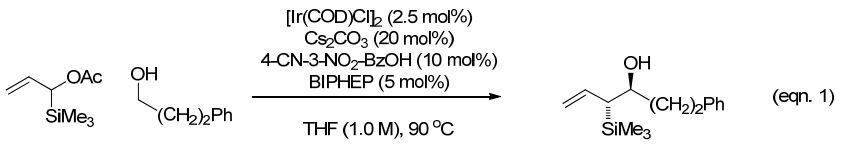


Scheme 2.1 Representative examples of chirally modified metal reagents for use in enantioselective carbonyl silylallylation.

In connection with studies aimed at the discovery of hydrogen-mediated reductive C-C bond formations beyond hydroformylation, a broad family of C-C bond forming transfer hydrogenations promoted by iridium catalyst was reported.[3] A remarkable feature of these processes resides in the ability to achieve carbonyl addition from the aldehyde or alcohol oxidation level. In the former case, isopropanol or formic acid mediate reductive C-C coupling. In the latter case, dehydrogenation of the primary alcohol reactants generates aldehyde electrophiles, while simultaneously driving reductive generation of nucleophilic organometallics from unsaturated reactants. Unlike conventional methods for carbonyl allylation, these processes circumvent use of premetallated nucleophiles and metallic reductants. In this fashion, α-(trimethylsilyl)allyl acetate can serve as a alternative to previously reported silicon-containing 1,3- or 1,1-bimetallic allyl transfer agents.

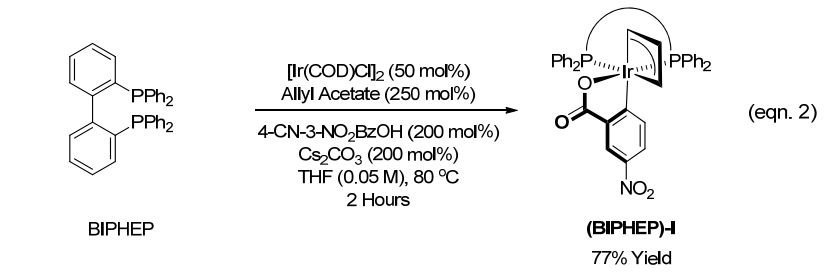
2.2 REACTION OPTIMIZATION

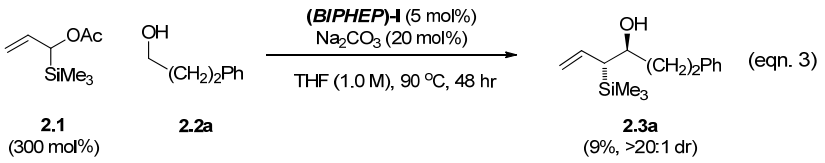
Our study began with the attempted (trimethylsilyl)allylation of alcohol **2.2a**. Using the *ortho*-cyclometallated catalyst generated *in situ* from $[Ir(cod)Cl]_2$, 4-cyano-3-nitrobenzoic acid, BIPHEP and allyl acetate, neither the desired (trimethylsilyl)allylation product **2.3a** or resulting Peterson olefination product was observed. (eqn. 1)



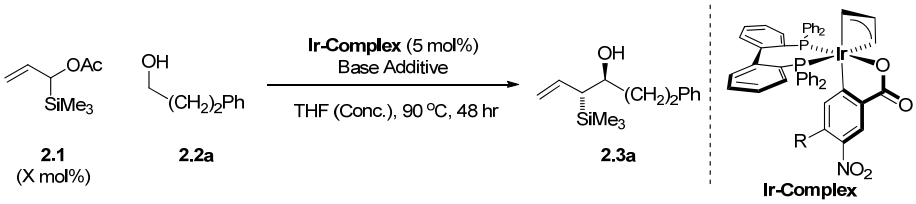
2.1 **2.2a** **2.3a** (eqn. 1)

Using the isolated π-allyl iridium precatalyst **(*BIPHEP*)-I** in the presence of cesium carbonate (eqn. 2), the desired (trimethylsilyl)allylation product **2.2a** was formed along with substantial quantities Peterson olefination product (eqn. 3).





Based on previous observations that the substituent *para* to the carboxylic group in our preformed cyclometallated catalyst plays an important role to affect the reaction outcome, we first screened different catalysts bearing various groups at this position. Our best result was obtained with cyano group on the *para* position of the acid moiety. In order to neutralize the acetic acid generated during C-C bond formation, a stoichiometric amount of base was added. This additive increased the conversion significantly. Additionally, due to the fact that the product tends to undergo Peterson type elimination under basic conditions, milder base such as $NaHCO_3$ was employed, and the yield increased dramatically, with excellent diastereoselectivity. Unfortunately, these conditions were not suitable for aromatic substrates (Table 2.1).

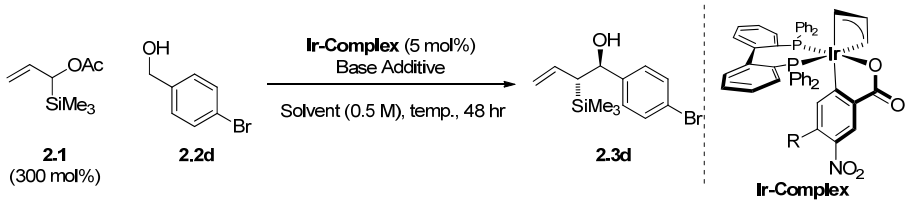


2.1 (X mol%) **2.2a** **2.3a** **Ir-Complex**

Entry	R	Base	Conc. (M)	eq. (mol%)	Yield (%)
1	H	Na_2CO_3 (20 mol%)	1.0	200	9 (>20:1 dr)
2	Cl	Na_2CO_3 (20 mol%)	1.0	200	13 (>20:1 dr)
3	CN	Na_2CO_3 (20 mol%)	1.0	200	22 (>20:1 dr)
4	CN	Na_2CO_3 (40 mol%)	1.0	200	30 (>20:1 dr)
5	CN	Na_2CO_3 (100 mol%)	1.0	200	40 (>20:1 dr)
6	CN	Na_2CO_3 (100 mol%)	0.5	200	49 (>20:1 dr)
7	CN	Na_2CO_3 (100 mol%)	0.2	200	36 (>20:1 dr)
8	CN	$NaHCO_3$ (100 mol%)	0.5	200	60 (>20:1 dr)
9	**CN**	**$NaHCO_3$ (100 mol%)**	**0.5**	**300**	**64 (>20:1 dr)**

Table 2.1 Optimization of inorganic base and substituents on Ir-complex.

Based on these result, we used *p*-bromobenzyl alcohol **2.2d** as a model substrate. We were pleased to find that K_3PO_4 also provided great enhancement of catalytic activity in our system. This helped us to carry out the reactions at lower temperature to achieve higher level of diastereoselectivity with better yield (Table 2.2).

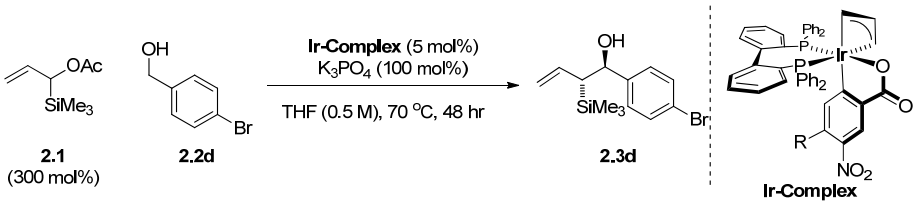


Entry	Solvent	Base	temp. (°C)	Yield (%)
1	THF	$NaHCO_3$ (100 mol%)	90	45% (10:1 dr)
2	THF	$NaHCO_3$ (100 mol%)	80	53% (10:1 dr)
3	2-Me-THF	$NaHCO_3$ (100 mol%)	80	33% (10:1 dr)
4	Dioxane	$NaHCO_3$ (100 mol%)	80	43% (10:1 dr)
5	Toluene	$NaHCO_3$ (100 mol%)	80	trace
6	*t*-Amylalcohol	$NaHCO_3$ (100 mol%)	80	trace
7	THF	-	80	trace
8	THF	NaH_2PO_4 (100 mol%)	80	trace
9	THF	Na_2HPO_4 (100 mol%)	80	trace
10	THF	Na_3PO_4 (100 mol%)	80	34% (10:1 dr)
11	THF	KH_2PO_4 (100 mol%)	80	12% (10:1 dr)
12	THF	K_3PO_4 (100 mol%)	80	69% (10:1 dr)
13	**THF**	**K_3PO_4 (100 mol%)**	**70**	**75% (>20:1 dr)**
14	THF	K_3PO_4 (100 mol%)	60	68% (>20:1 dr)

Table 2.2 Optimization of inorganic base, solvents and temperature.

When screening phosphates as base additives, we found an interesting observation: different methods for drying base additives provided different reaction outcomes. For example, drying the base in oven for three days provided good yield and excellent diastereoselectivity. However, when we used flame dried base additive, only a trace amount of desired product was obtained and significant amount of Peterson Olefination by-product had been formed. Based on the hygroscopic nature of K_3PO_4, we hypothesized that the oven-dried base was contaminated with some water. Hence we used water as an additive in our catalytic system, and started to screen water loading. Finally, when 500 mol% water was added to the reaction mixture, the desired product was obtained in 78% yield, with > 20:1 *anti*:*syn* d.r. (Table 2.3). Later study showed that water could also help other iridium catalyzed carbon-carbon bond formation reactions using the *o*-cyclometallated iridium *C,O*-benzoate as catalyst. The origin of this water

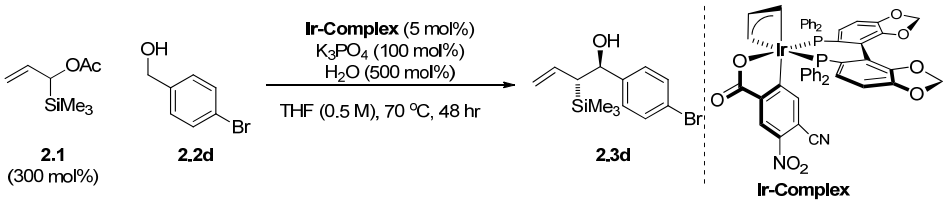
effect has not yet been fully investigated; it might be that water helped to modify the *p*H in the reaction mixture, increase the solubility of the inorganic base and/or work as a proton shuttle to increase the turnover rate.



	Entry	Additive	Yield (%)
Oven Dried!	1	-	75% (>20:1 dr)
Flame Dried!	2	-	trace
	3	H_2O (50 mol%)	trace
	4	H_2O (100 mol%)	12% (>20:1 dr)
	5	**H_2O (500 mol%)**	**78% (>20:1 dr)**
	6	H_2O (1000 mol%)	67% (>20:1 dr)

Table 2.3 Observation of Water Effect.

After successfully designing iridium catalyzed diastereoselective carbonyl silylallylation, we applied (*R*)-Segphos modified preformed *ortho*-cyclometallated iridium *C,O*-benzoate instead of the racemic Biphep complex in our reactions, after changing the concentration from 0.5 M to 1.0 M, a yield with 72%, > 20:1 *anti*:*syn* d.r., 95% e.e. was achieved (Table 2.4).



Entry	Conc. (M)	temp. (°C)	Yield (%)	ee (%)
1	0.5	70	62% (>20:1 dr)	95
2	0.5	80	35% (>20:1 dr)	92
3	**1.0**	**70**	**72% (>20:1 dr)**	**95**

Table 2.4 Optimization for enantioselectivity.

With the optimized condition in hand, the scope of this transformation was tested. Diverse substituted benzyl alcohols, hetero aromatic alcohols, allylic alcohols and, unactivated aliphatic alcohols all showed good reactivity in this system, having an excellent level of *anti*-diastereo- and enantioselectivity. Carbonyl silylallylation from the aldehyde oxidation level employing isopropanol as the terminal reductant has also been explored. Under identical condition, but in the presence of isopropanol, corresponding aldehydes were converted to silylallylation products in good yield and high levels of *anti*-diastereoselectivity with exceptional levels of enantioselectivity (Table 2.5).

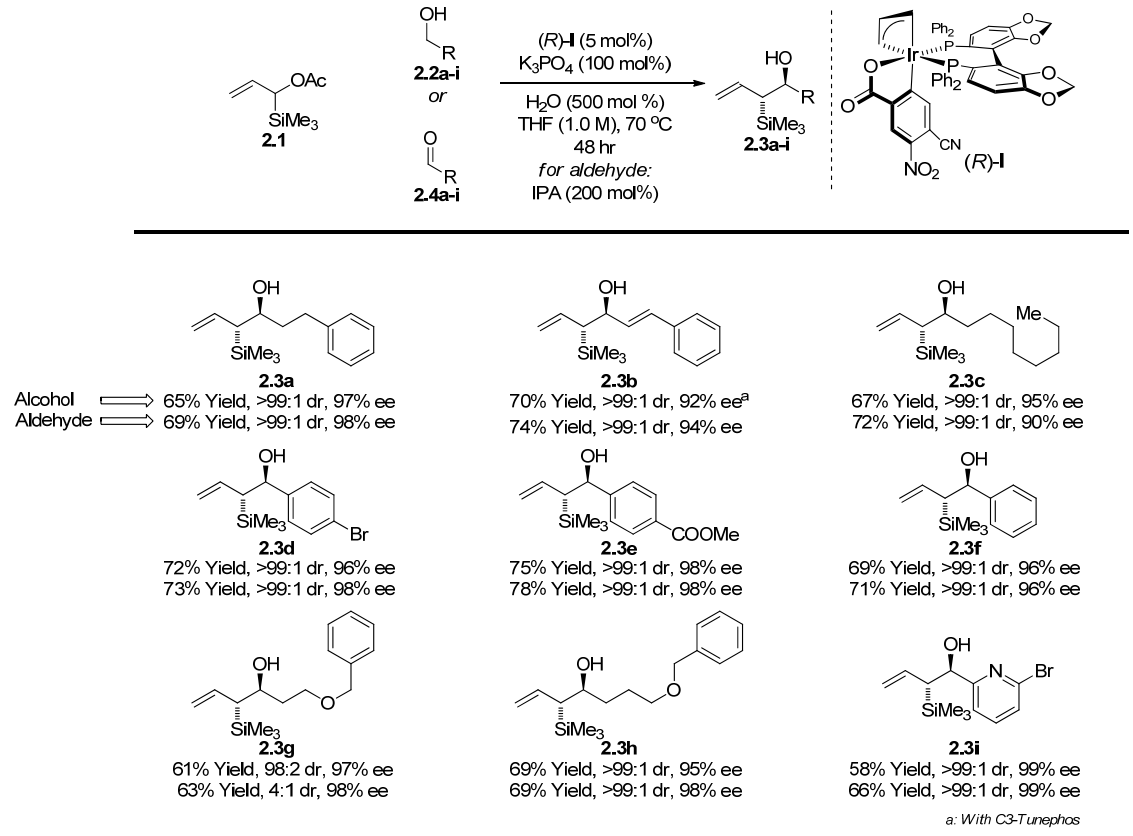
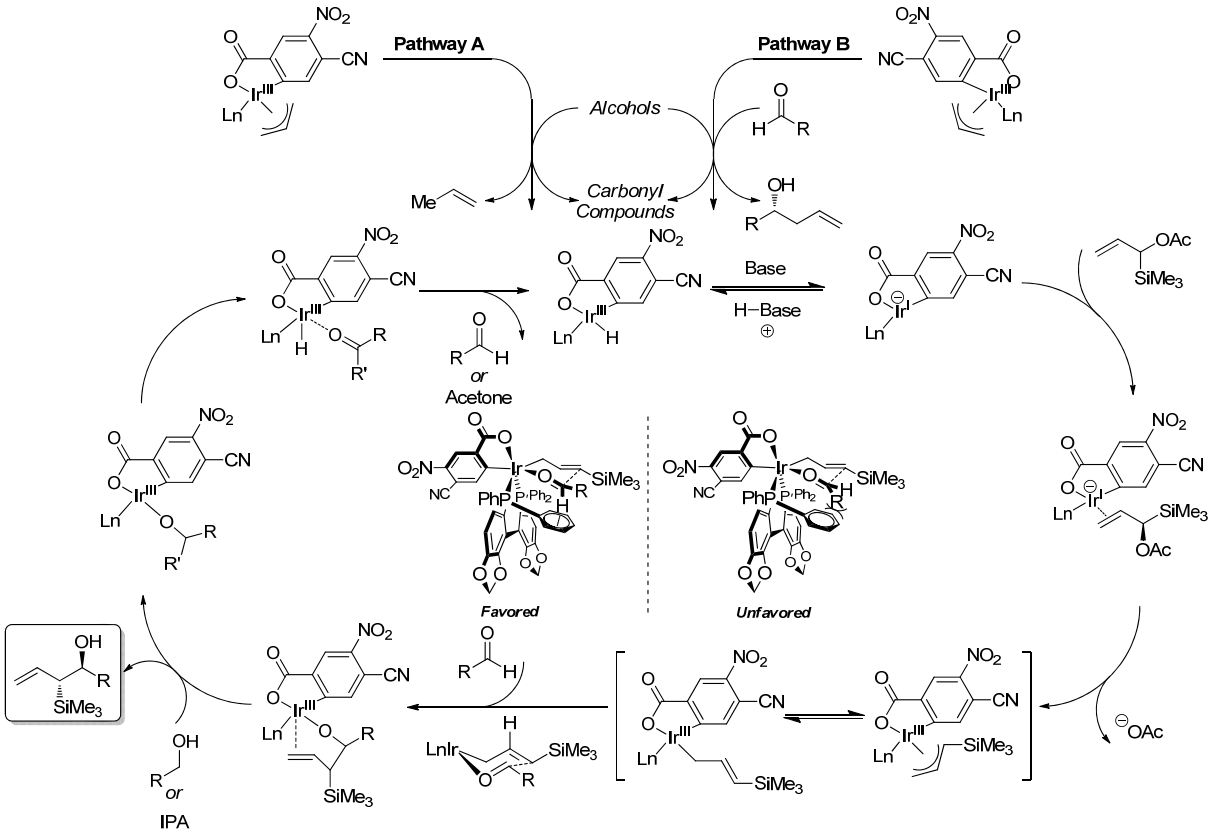


Table 2.5 Enantioselective α-(trimethylsilyl)allylation.

A plausible catalytic cycle is shown below. In order to activate the preformed iridium allyl complex, various pathways are possible. Protonolysis of the metal-allyl bond by alcohol presented (*Pathway A*), or transferring the allyl group to aldehyde (*Pathway B*) should be most plausible to generate the iridium hydride. Deprotonation of the iridium hydride with base generates a nucleophilic iridium anion, which coordinates to silylallyl acetate. Ionization of the silylallyl acetete through an S_N2' pathway gives the kinetically favored *cis*-π-silylallyl complex, which is in fast equilibrium with the (*E*)-silylallyl complex and opens a vacant site on the metal center. (Scheme 2.2)



Scheme 2.2 Proposed Catalytic Mechanisms and Model Accounting for Observed Stereocontrol.

At this stage, the aldehyde coordinates with iridium and carbon-carbon bond formation occurs through a six-membered chair-like transition state. This proposed transition state model is necessary to achieve a high level of stereocontrol. The newly formed iridium homoallylic alkoxide is a *hexa*-coordinated 18-electon complex, which suppresses the β-hydride elimination pathway. Another molecule of alcohol comes in to hydrolyze this complex, releases the desired product and, regenerates the iridium hydride to finish the catalytic cycle (Scheme 2.2). The absolute stereochemistry of the adducts has been confirmed by comparing the optical rotation with literature reported compound (See Supporting Information).

By far, we have developed a highly stereoselective silylallylation method under iridium catalyzed transfer hydrogenation conditions. Notably, the manipulation of pre-activation is dramatically shorter than previously reported methods, the reaction is not moisture sensitive and, excellent levels of regio-, *anti*-diastereo- and enantioselectivity are achieved using chiral catalyst under relatively easy-to-handle temperatures.

2.3 APPLICATIONS OF ADDUCTS

To evaluate the utility of the coupling products **2.3a**-**2.3i**, adducts **2.3a**, **2.3c**, **2.3f** and **2.3g** were subjected to DMDO-mediated oxidative elimination.[1m,n] The 1,4-ene-diols **2.5a**, **2.5c**, **2.5f** and **2.5g** were produced in excellent yield with high levels of E:Z selectivity (Table 2.6).

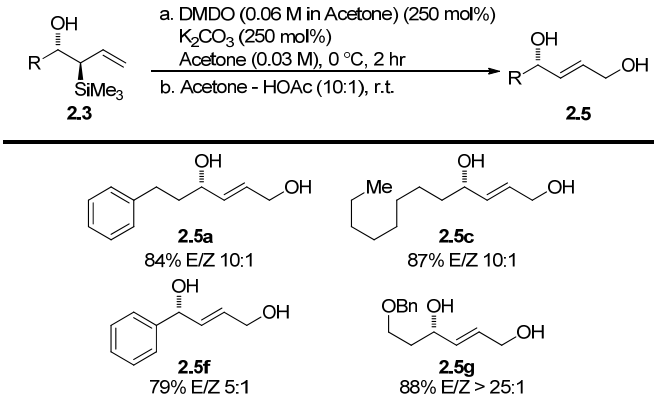
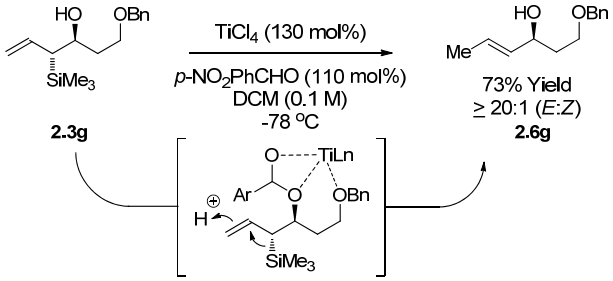


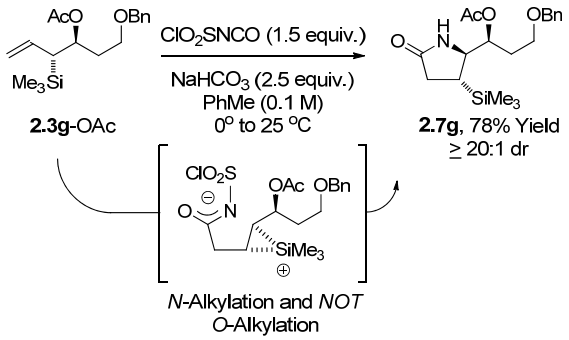
Table 2.6 Dioxirane mediated oxidative desilylation of adducts to furnish the corresponding 1,4-ene-diols.

Proto-desilylation was attempted next. Under nearly all conditions assayed, exclusive formation of Peterson olefination products was observed. However, upon exposure of adduct **2.3g** to $TiCl_4$ in the presence of exogenous aldehyde, the product of proto-desilylation **2.6g** is generated in 73% yield with complete *E*:*Z* selectivity (Scheme 2.3). In the absence of aldehyde, Peterson olefination is again the exclusive reaction product, suggesting exogenous aldehyde protects the hydroxyl moiety of **2.3g** through formation of a titanium bound hemi-acetal. Notably, compound **2.6g** was previously prepared in 7-steps from malic acid.[4] Thus far, the protodesilylation is most efficient for the benzyl ether-containing adduct **2.6g**.



Scheme 2.3 Protodesilylation of requires exogenous aldehyde.

Finally, under condition similar to those described by Woerpel,[5] exposure of **2.5g**-OAc to chlorosulfonyl isocyanate delivers the product of [3+2] cycloaddition, the 4,5-*trans*-disubstituted pyrrolidinone **2.7g**, as a single diastereomer. Lactone formation was not observed. Formation of the 2**.7g** suggests a mechanism involving stereoselective addition of chlorosulfonyl isocyanate to the allylsilane *anti*-periplanar with respect to the silyl group to generate the indicated *β*-silyl carbocation. Exclusive *N*-cyclization accompanied by 1,2-silyl migration delivers the 4,5-*trans*-substituted pyrrolidinone **2.7g**. In the absence of $NaHCO_3$, a mixture of lactone and lactam products are observed. These data suggest that partitioning of the *N*- and *O*-cyclization pathways is not dictated primarily by steric factors as proposed by Woerpel,[5b] but that the acidity of the medium plays a dominant role (Scheme 2.4)



Scheme 2.4 Reaction of adduct with chlorosulfonyl isocyanate to furnish the product of formal [3+2] cycloaddition

2.4 SUMMARY

We report a method for highly *anti*-diastereo- and enantioselective carbonyl silylallylation under the conditions of iridium catalyzed transfer hydrogenation from both aldehyde and alcohol oxidation levels. Substituted 1,4-ene-diols, five-membered lactam,

and formal vinylation products can be obtained after simple manipulations. The corresponding reaction using ruthenium based catalyst and allenylsilanes as allyl donors is still under way.

2.5 EXPERIMENTAL SECTION

General Methods

All reactions were run under an atmosphere of Argon. Tetrahydrofuran (THF) and toluene were obtained from Pure-Solv MD-5 Solvent Purification System (Innovative Technology). Anhydrous solvents were transferred by an oven-dried syringe. Sealed tubes (13x100 mm) were purchased from Fischer Scientific and were dried in an oven overnight and cooled under a stream of nitrogen prior to use. Commercially available allyl acetate (Aldrich) was purified by distillation prior to use. Cesium carbonate was purchased from Alfa Aesar and was used directly without further purification. Isopropanol (Fisher) was purified by distillation prior to use. Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F_{254}). Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M or M-H) or a suitable fragment ion. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) spectra were recorded with a Varian Gemini (400 MHz) spectrometer for $CDCl_3$ solutions and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δ_H (7.26 ppm) and $CDCl_3$ δ_C (77.0 ppm), respectively, as internal standards. Coupling constants are reported in Hertz (Hz).

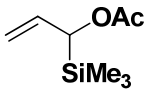
Preparation of (*R*)-I

To a mixture of $[Ir(cod)Cl]_2$ (87.3 mg, 0.13 mmol, 100 mol%), (*R*)-SEGPHOS (159 mg, 0.26 mmol, 200 mol%), Cs_2CO_3 (169 mg, 0.52 mmol, 400 mol%), 4-CN-3-NO_2BzOH (100 mg, 0.52 mmol, 400 mol%) and allyl acetate (65 mg, 0.65 mmol, 500 mol%) in a sealed tube under N_2 atmosphere was added THF (2.6 mL, 0.05 M). The reaction mixture was stirred for 30 min at ambient temperature and heated for 1.5 hr at 80 ^oC, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was filtered and washed with THF (10 mL). The filtrate was concentrated *in vacuo* and desolved in THF (2 mL), then hexanes (50 mL) was added. A yellow precipitate formed, which was collected by filtration and dried under vacuum (101 mg, 0.098 mmol, 75% yield).

Preparation of (*R*)-C3-TUNEPHOS

To a mixture of $[Ir(cod)Cl]_2$ (87.3 mg, 0.13 mmol, 100 mol%), (*R*)-C3-TUNEPHOS (155 mg, 0.26 mmol, 200 mol%), Cs_2CO_3 (169 mg, 0.52 mmol, 400 mol%), 4-CN-3-NO_2BzOH (100 mg, 0.52 mmol, 400 mol%) and allyl acetate (65 mg, 0.65 mmol, 500 mol%) in a sealed tube under N_2 atmosphere was added THF (2.6 mL, 0.05 M). The reaction mixture was stirred for 30 min at ambient temperature and heated for 1.5 hr at 80 ^oC, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was filtered and washed with THF (10 mL). The filtrate was concentrated *in vacuo* and desolved in THF (2 mL), then hexanes (50 mL) was added. A yellow precipitate formed, which was collected by filtration and dried under vacuum (103 mg, 0.101 mmol, 78% yield).

1-(trimethylsilyl)allyl acetate (2.1)



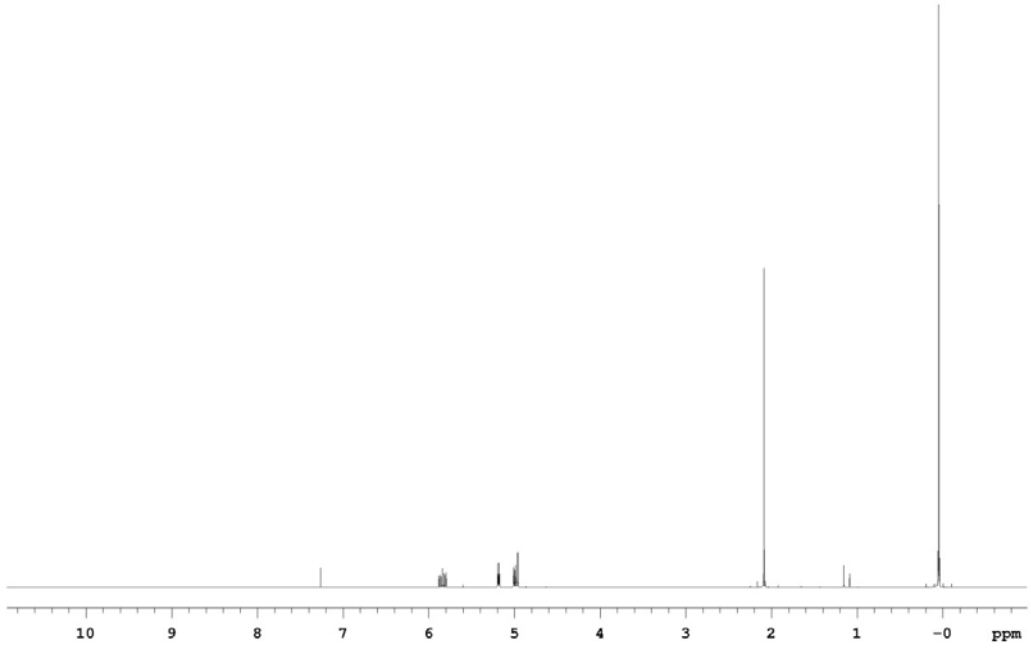
In accordane with a modified literature procedure,[6] tirmethylsilyl allyl ether (10.0 g, 0.076 mol, 100 mol%) was dissolved in THF (250 mL, 0.3 M), and then cooled to -78 ^{o}C. 1.7 M solution of *t*-butyllithium in pentane (51 mL, 0.087 mol, 115 mol%) was added dropwise over 15 min and the resulting bright yellow solution was stirred for 2 hr at -78 ^{o}C. The reaction mixture was quenched with acetic anhydride (8.025 g, 0.079 mol, 105 mol%) at -78 ^{o}C and then stirred at ambient temperature overnight. Thre resulting mixture was diluted with water (50 mL) and pentane (100 mL). The organic phase was separated and washed with water (3 times) and brine. The resulting solution was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; Pentane: Ether, 20:1) provied **2.1** (9.2 g, 0.053 mmol) as a pale yellow oil in 70% yield.

TLC (SiO_2): R_f = 0.6 (ethyl acetate: hexanes, 1:30).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88-5.80 (m, 1H), 5.18 (dt, *J* = 5.6, 2.0 Hz, 1H), 5.00 (dt, *J* = 8.4, 2.0 Hz, 1H), 4.97-4.95 (m, 1H), 2.09 (s, 3H), 0.05 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 134.9, 111.2, 70.5, 21.0, -4.1.

FTIR (neat): υ 2960, 1739, 1634, 1408, 1369, 1230, 1159, 1086, 1017, 991, 901, 839, 785, 752, 722, 696.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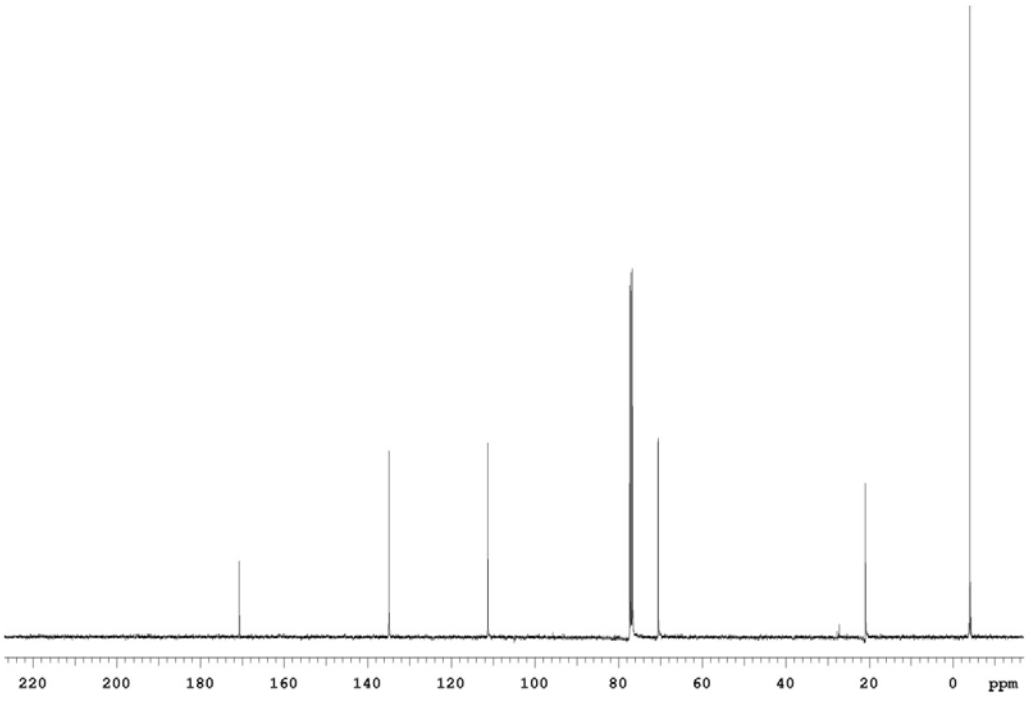
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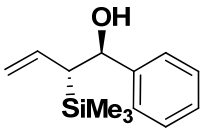
(1*S*,2*R*)-1-phenyl-2-(trimethylsilyl)but-3-en-1-ol (2.3e)



An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with benzaldehyde **2.4e** (21.2 mg, 0.20 mmol, 100 mol%), *(R)*-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%), isopropanol (24 mg, 0.4 mmol, 200 mol%) and α-(trimethylsilyl)allyl acetate (103 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **2.3e** (31.3 mg, 0.142 mmol) as a colorless oil in 71% yield.

TLC (SiO_2): R_f = 0.3 (ethyl acetate: hexanes, 1:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.24 (m, 5H), 5.86 (dt, *J* = 17.2, 10.4 Hz, 1H), 5.11 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.05-5.00 (m, 1H), 4.80 (dd, *J* = 8.4, 1.6 Hz, 1H), 2.21 (d, *J* = 1.6 Hz, 1H), 2.10-2.05 (m, 1H), -0.20 (s, 9H).

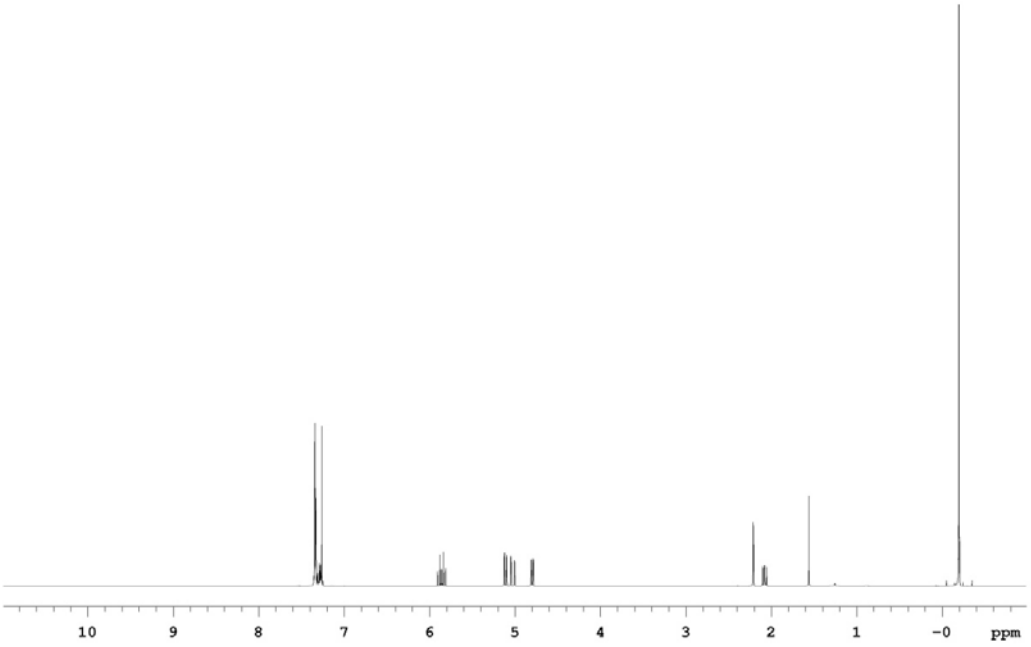
^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 136.6, 128.4, 127.8, 126.9, 116.0, 74.5, 45.6, -2.4.

HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 210 nm), t_{minor} = 11.0 min, t_{major} = 11.6 min; ee = 96%.

$[\alpha]_D^{25}$= +47.01 (c =2.8, $CHCl_3$). To corroborate the assignement of absolute stereochemistry, the optical rotation was correlated with a known compound[7]

FTIR (neat): υ 3426, 2953, 2896, 1626, 1494, 1455, 1386, 1247, 1196, 1153, 1089, 1050, 1028, 988, 906, 835, 786, 763, 718, 698 cm^{-1}.

HRMS (CI) Calcd. for $C_{13}H_{21}OSi$ $[M+H]^+$: 221.1362, Found: 221.1356.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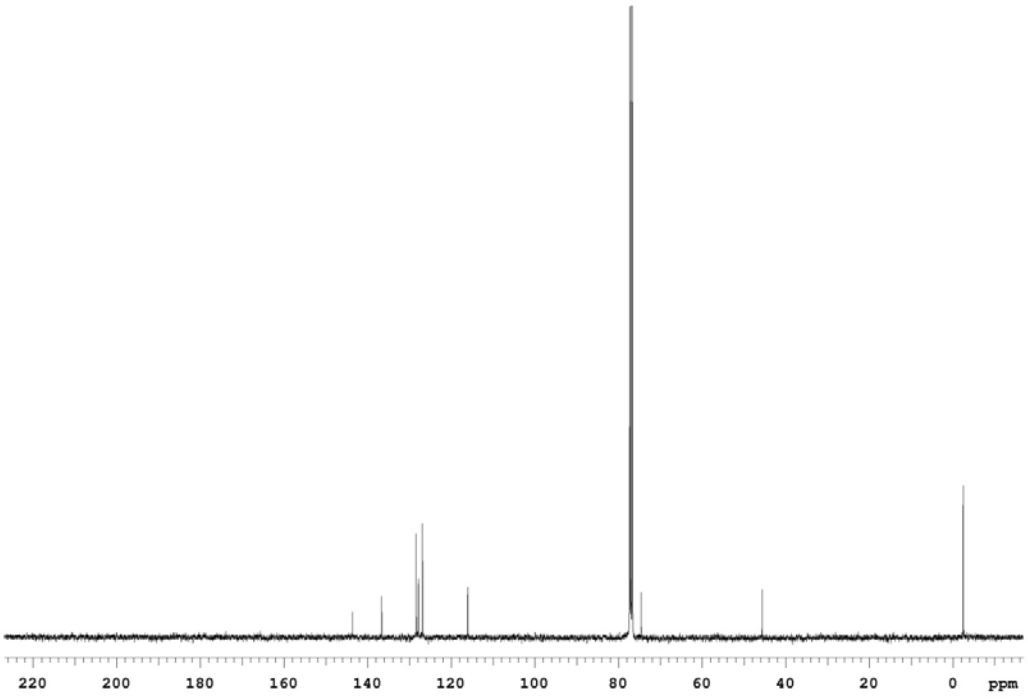
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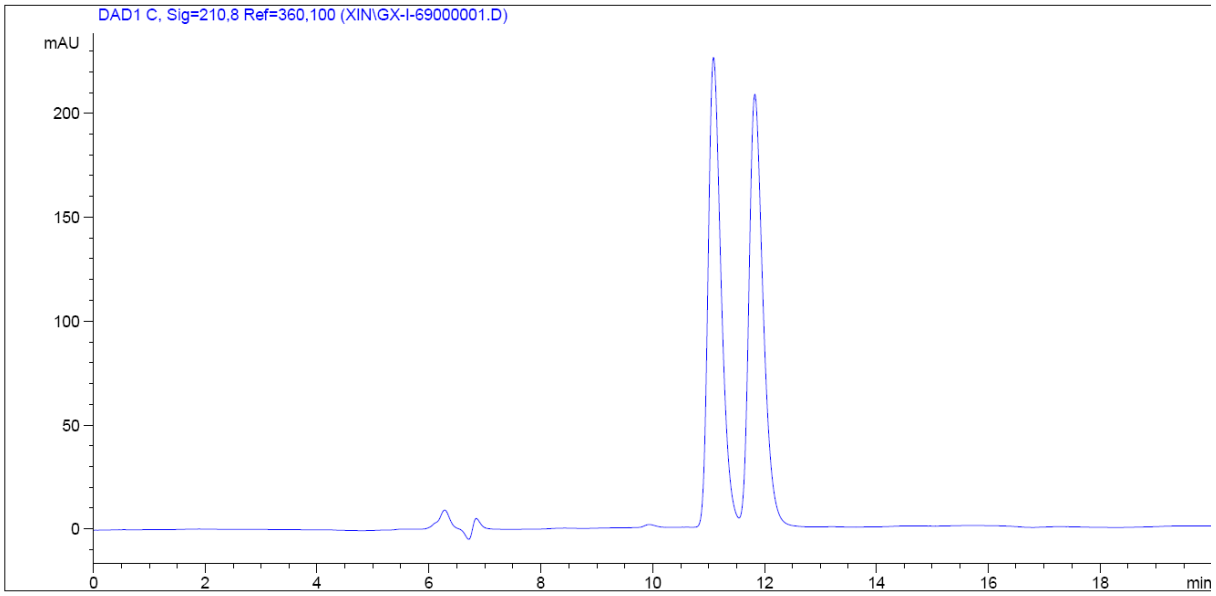

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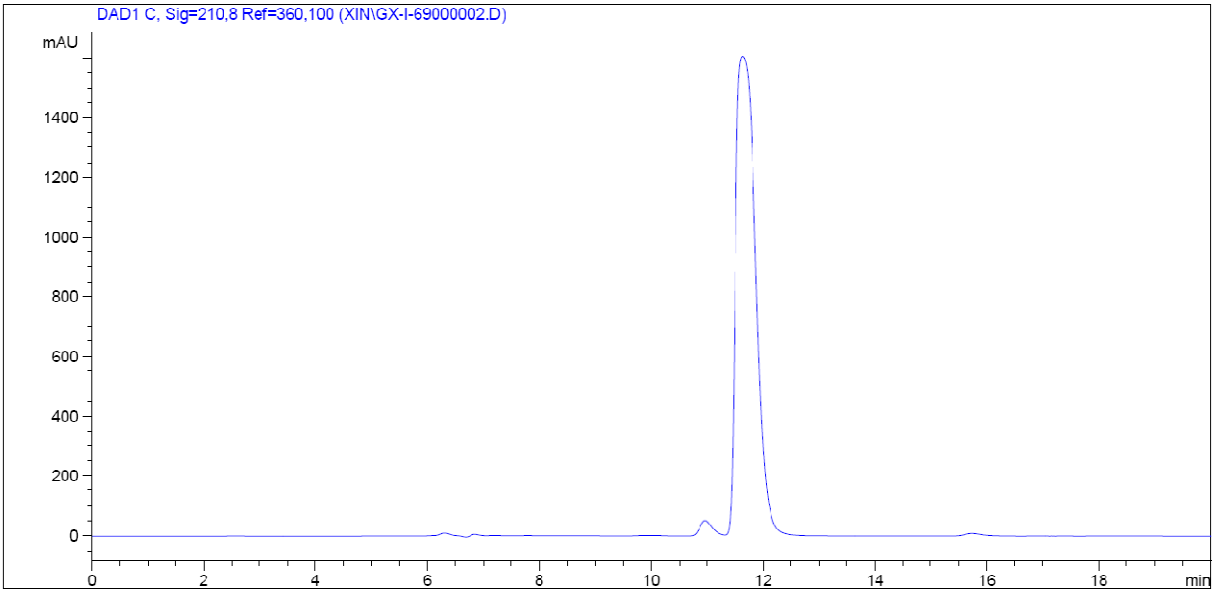


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.961	VV	0.2394	804.91974	51.20407	1.9935
2	11.633	VB	0.3976	3.95727e4	1605.10217	98.0065

(1*S*,2*R*)-1-(4-bromophenyl)-2-(trimethylsilyl)but-3-en-1-ol (2.3d)

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 4-bromobenzaldehyde **2.4d** (37.0 mg, 0.20 mmol, 100 mol%), *(R)*-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%), isopropanol (24 mg, 0.4 mmol, 200 mol%) and α-(trimethylsilyl)allyl acetate (103 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **2.3d** (43.7 mg, 0.146 mmol) as a colorless oil in 73% yield.

TLC (SiO_2): R_f = 0.3 (ethyl acetate: hexanes, 1:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.4, 2H), 7.46 (d, *J* = 8.4, 2H), 5.82 (dt, *J* = 17.2, 10.4 Hz, 1H), 5.10 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.03 (d, *J* = 17.2 Hz, 1H), 4.78 (d, *J* = 7.6 Hz, 1H), 2.20 (br, 1H), 2.02-1.97 (m, 1H), -0.16 (s, 9H).

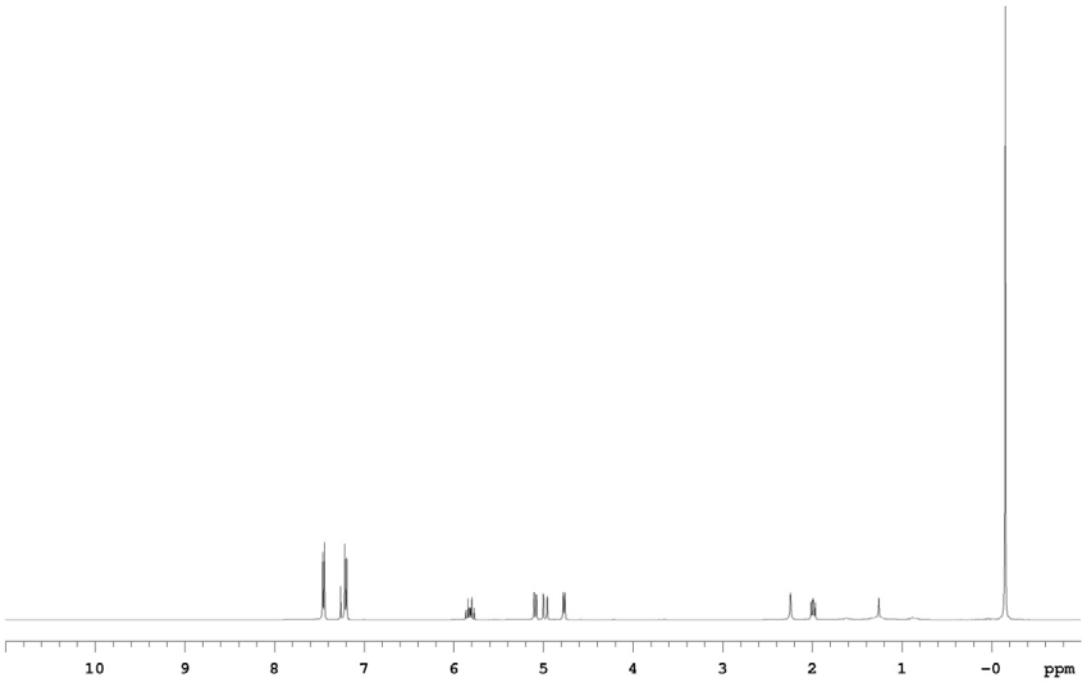
^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 135.9, 131.4, 128.5, 121.4, 116.3, 73.8, 45.5, -2.6.

HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 210 nm), t_{minor} = 11.9 min, t_{major} = 12.9 min; ee = 98%.

$[\alpha]_D^{25}$= +37.4 (c =0.62, CH_2Cl_2).

FTIR (neat): υ 3430, 2953, 1625, 1592, 1485, 1408, 1247, 1191, 1155, 1088, 1070, 1010, 908, 833, 785, 753, 737, 691 cm^{-1}.

HRMS (CI) Calcd. for $C_{13}H_{20}BrOSi$ $[M+H]^+$: 299.0467, Found: 209.0470.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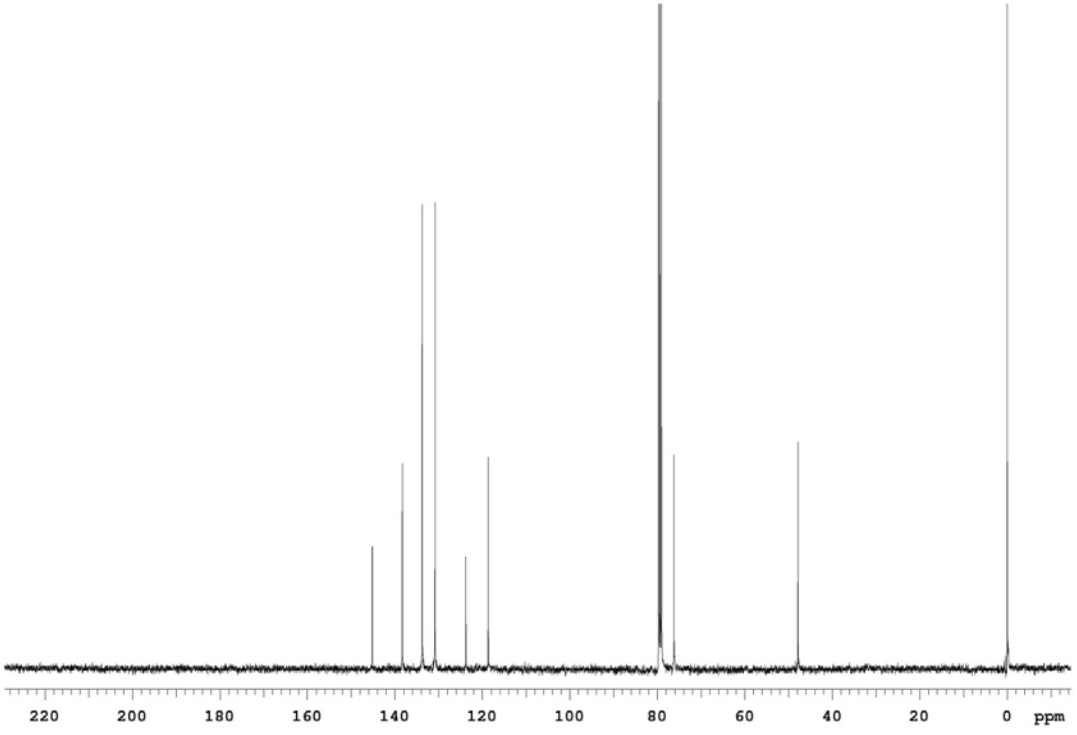
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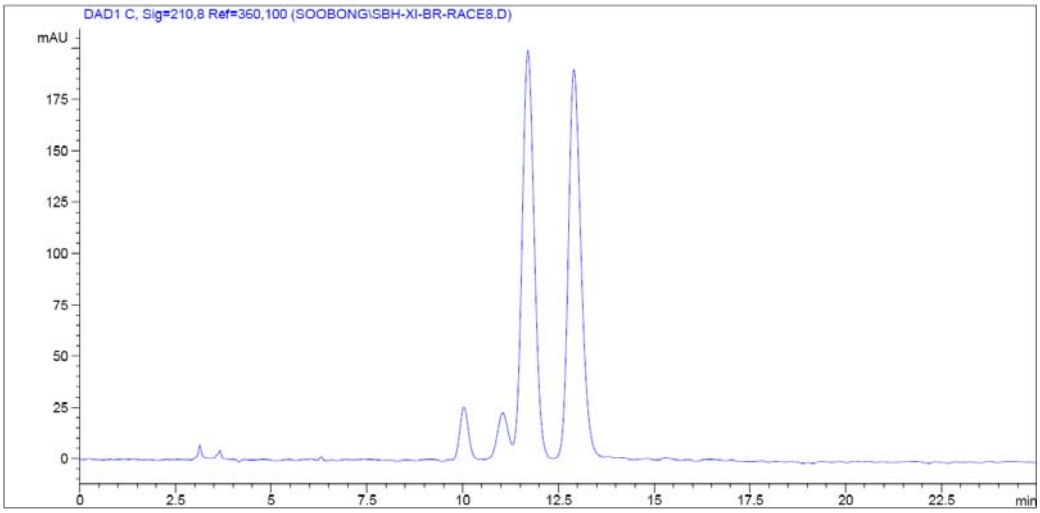

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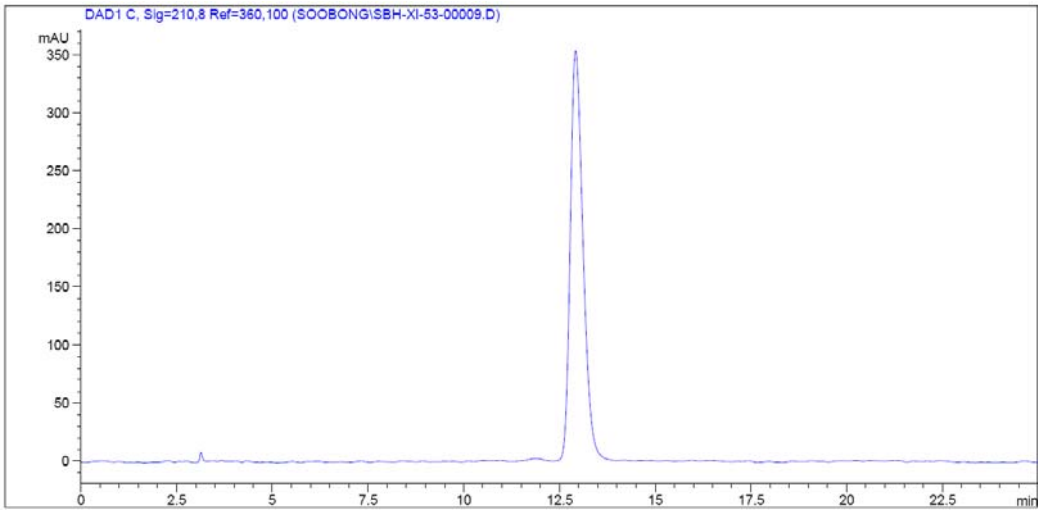
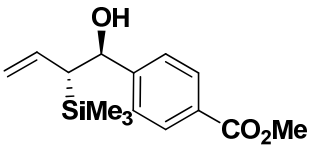
4	12.903	VB	0.3555	4520.55859	191.44574	45.3965



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.861	BV	0.3397	70.18861	2.51388	0.8478
2	12.919	VB	0.3590	8209.10840	353.43179	99.1522

methyl 4-((1S,2R)-1-hydroxy-2-(trimethylsilyl)but-3-enyl)benzoate (2.3e)



An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with methyl 4-formylbenzoate **2.4e** (32.8 mg, 0.20 mmol, 100 mol%), *(R)*-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%), isopropanol (24 mg, 0.4 mmol, 200 mol%) and α-(trimethylsilyl)allyl acetate (103 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **2.3e** (43.4 mg, 0.156 mmol) as a colorless oil in 78% yield.

TLC (SiO_2): R_f = 0.2 (ethyl acetate: hexanes, 1:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01-7.99 (m, 2H), 7.41-7.39 (m, 2H), 5.83 (dt, *J* = 16.8, 10.4 Hz, 1H), 5.08 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.99-4.94 (m, 1H), 4.88 (d, *J* = 7.6 Hz, 1H), 3.91 (s, 3H), 2.27 (br, 1H), 2.04-2.00 (m, 1H), -0.15 (s, 9H).

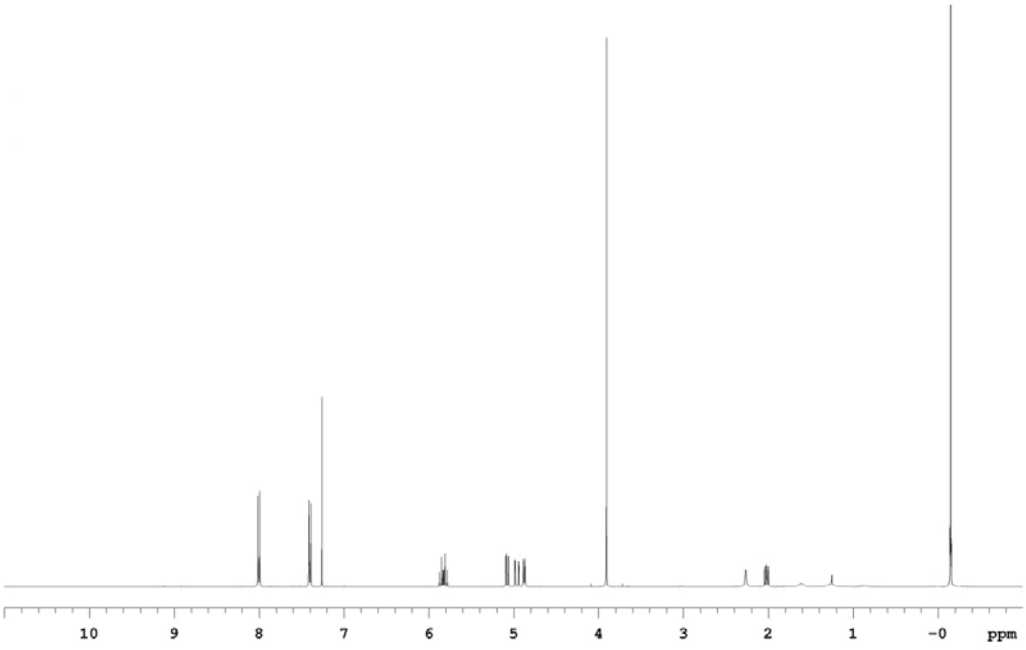
^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 149.0, 135.7, 129.7, 129.4, 126.7, 116.4, 74.1, 52.1, 45.5, -2.4.

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 230 nm), t_{minor} = 12.7 min, t_{major} = 14.3 min; ee = 98%.

$[\alpha]_D^{25}$= +16.1 (c =0.23, CH_2Cl_2).

FTIR (neat): υ 3501, 2954, 2889, 1698, 1624, 1609, 1433, 1390, 1346, 1307, 1155, 1018, 1005, 977, 955, 895, 835, 784, 772, 729, 702 cm^{-1}.

HRMS (CI) Calcd. for $C_{15}H_{23}O_3Si$ $[M+H]^+$: 279.1416, Found: 279.1417.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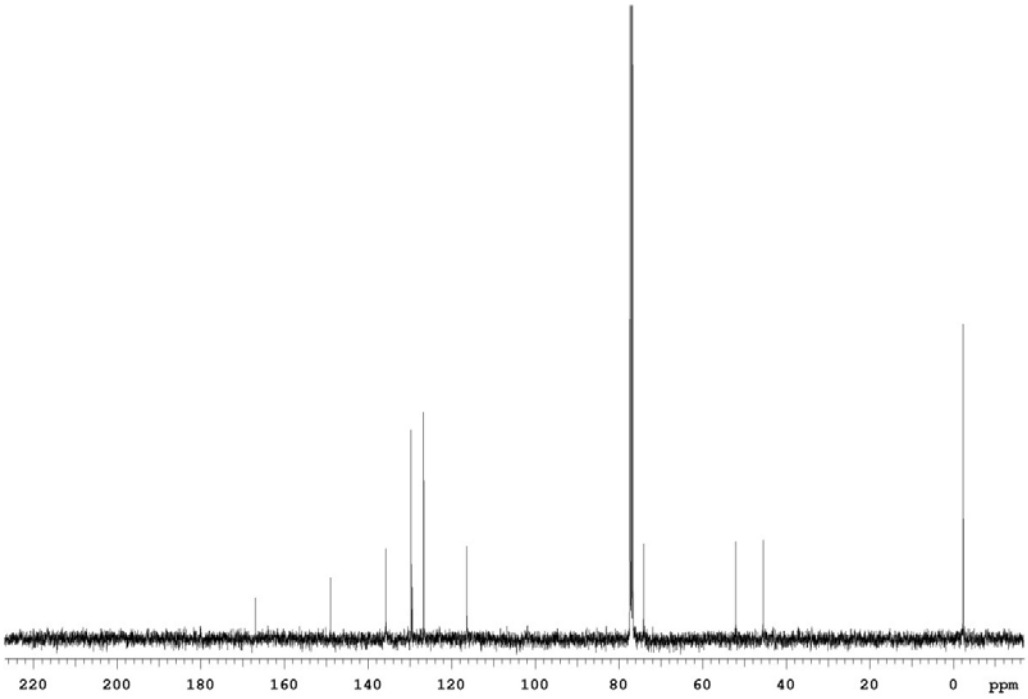
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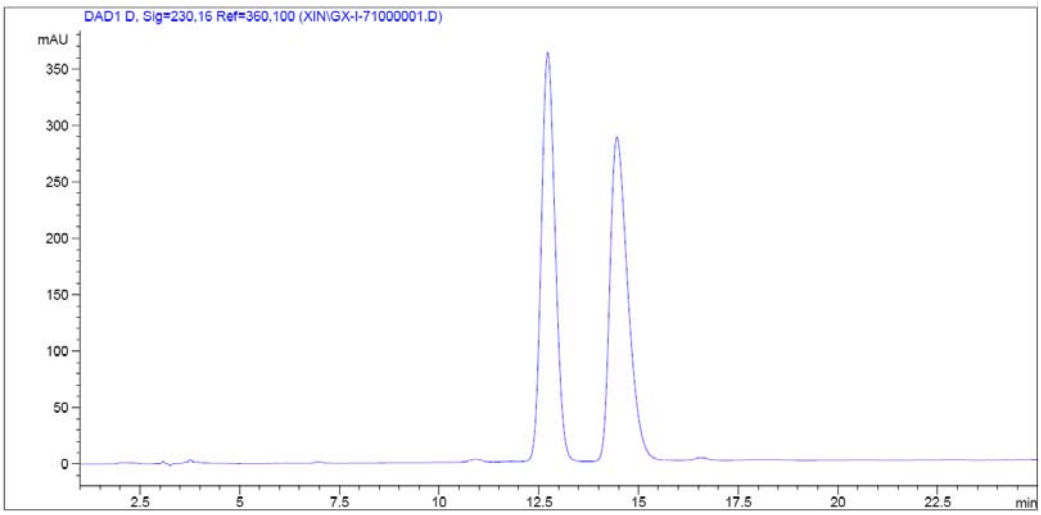

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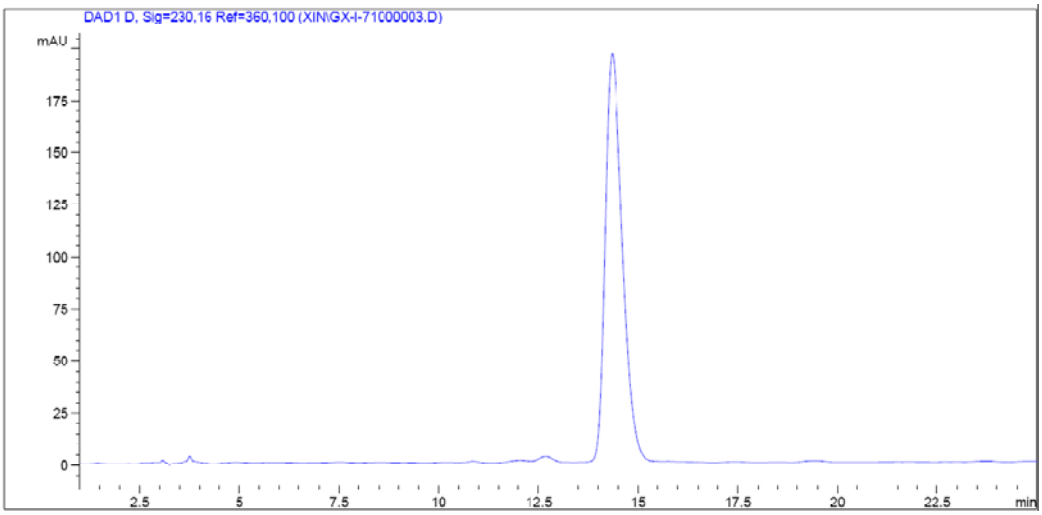

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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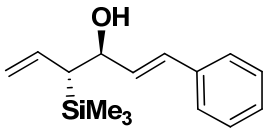
2	14.348	BB	0.4583	5857.12500	196.21809	99.0409

(3*S*,4*R*,*E*)-1-phenyl-4-(trimethylsilyl)hexa-1,5-dien-3-ol (2.3b)



An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with cinnamaldehyde **2.4b** (26.4 mg, 0.20 mmol, 100 mol%), *(R)*-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%), isopropanol (24 mg, 0.4 mmol, 200 mol%) and α-(trimethylsilyl)allyl acetate (103 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **2.3b** (36.5 mg, 0.148 mmol) as a colorless oil in 74% yield.

TLC (SiO_2): R_f = 0.2 (ethyl acetate:hexanes, 1:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.22 (m, 5H), 6.58 (d, *J* = 15.6 Hz, 1H), 6.22 (dd, *J* = 15.6, 7.6 Hz, 1H), 5.84 (dt, *J* = 16.8, 10.4 Hz, 1H), 5.10 (dd, *J* = 10.0, 2.0 Hz, 1H), 5.02 (ddd, *J* = 16.8, 2.0, 0.8 Hz, 1H), 4.43 (td, *J* = 7.6, 1.2 Hz, 1H), 1.90-1.86 (m, 2H), 0.05 (s, 9H).

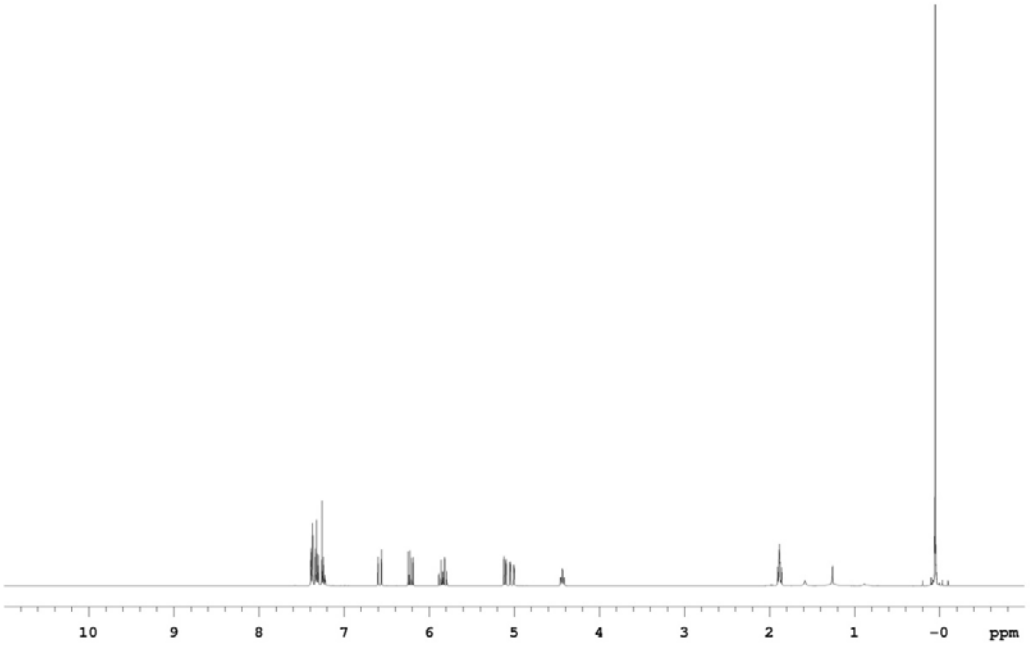
^{13}C NMR (100 MHz, $CDCl_3$): δ 136.6, 136.1, 131.9, 130.8, 128.6, 127.7, 126.5, 115.7, 73.2, 44.1, -1.9.

HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 210 nm), t_{minor} = 13.6 min, t_{major} = 14.8 min; ee = 94%.

$[\alpha]_D^{25}$= +38.8 (c =0.21, CH_2Cl_2).

FTIR (neat): υ 3428, 3026, 2954, 1625, 1494, 1449, 1379, 1246, 1105, 1035, 1003, 964, 897, 860, 853, 784, 748, 724, 691 cm^{-1}.

HRMS (CI) Calcd. for $C_{15}H_{23}OSi$ $[M+H]^+$: 247.1518, Found: 247.1520.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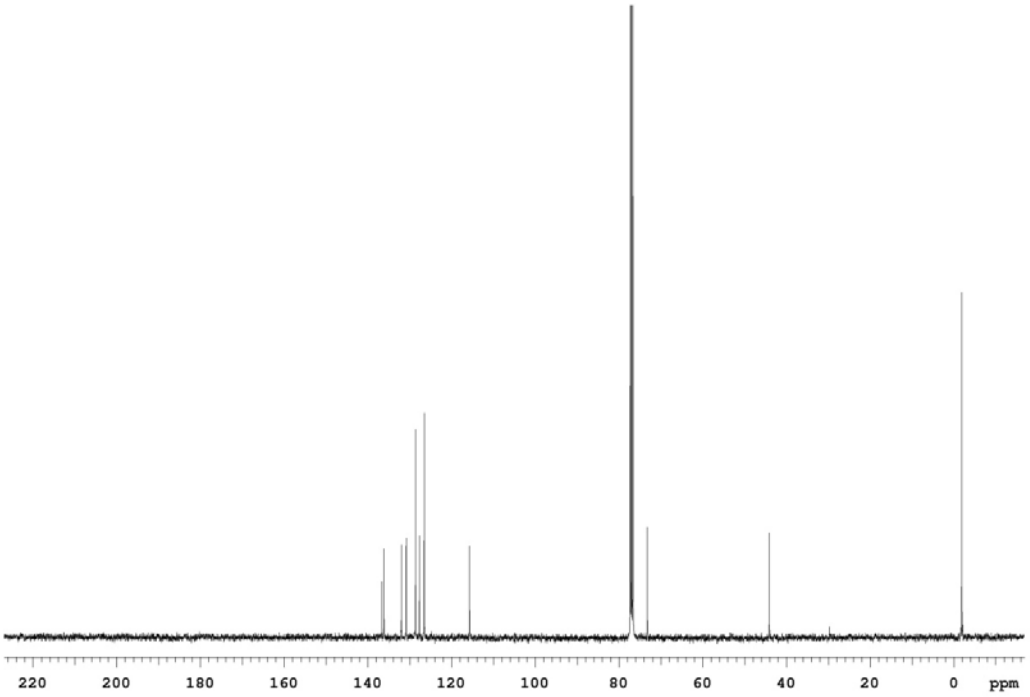
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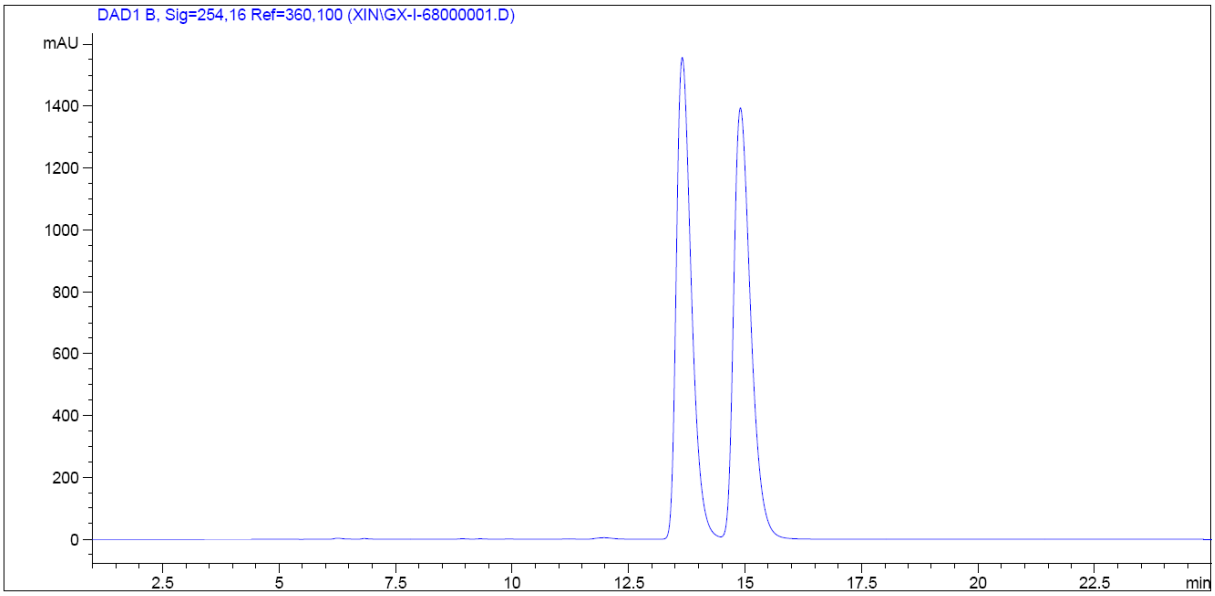
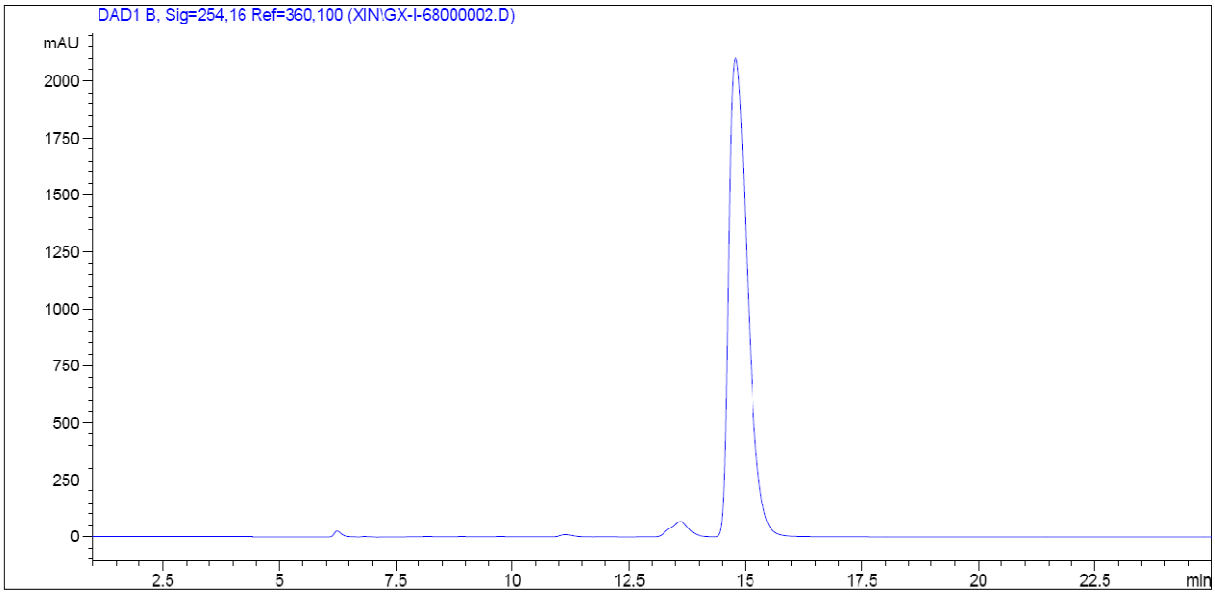


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.650	BV	0.3460	3.49861e4	1557.74707	49.7498
2	14.898	VB	0.3875	3.53381e4	1395.15076	50.2502



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.599	VV	0.3967	1900.46570	68.29153	3.1424
2	14.787	VV	0.4367	5.85783e4	2104.55469	96.8576

(1*S*,2*R*)-1-(6-bromopyridin-2-yl)-2-(trimethylsilyl)but-3-en-1-ol (2.3i)

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 6-bromopicolinaldehyde **2.4i** (37.2 mg, 0.20 mmol, 100 mol%), *(R)*-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%), isopropanol (24 mg, 0.4 mmol, 200 mol%) and α-(trimethylsilyl)allyl acetate (103 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **2.3i** (39.6 mg, 0.132 mmol) as a colorless oil in 66% yield.

TLC (SiO_2): R_f = 0.2 (ethyl acetate:hexanes, 1:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (t, *J* = 7.6 Hz, 1H), 7.34 (dd, *J* = 7.6, 0.4 Hz, 1H), 7.20 (dt, *J* = 7.6, 0.4 Hz, 1H), 5.71 (dt, *J* = 17.2, 10.4 Hz, 1H), 4.94 (t, *J* = 4.4 Hz, 1H), 4.85 (dd, *J* = 10.4, 2.4 Hz, 1H), 4.76 (ddd, *J* = 17.2, 2.4, 0.8 Hz, 1H), 3.59 (d, *J* = 4.4 Hz, 1H), 2.07 (dd, *J* = 10.4, 4.4 Hz, 1H), 0.05 (s, 9H).

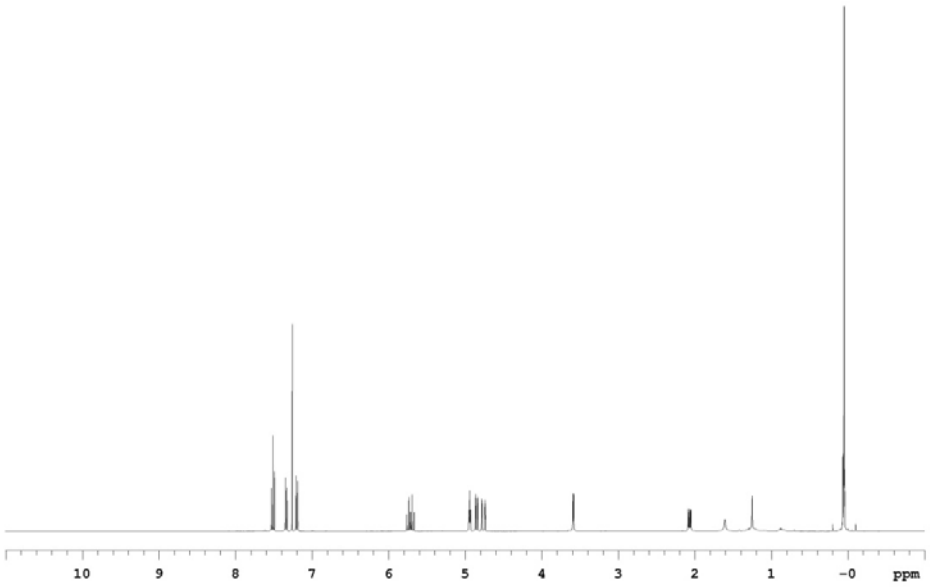
^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 140.7, 138.8, 134.7, 126.3, 119.6, 114.9, 73.0, 43.4, -2.3.

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 98:2, 1.0 mL/min, 254 nm), t_{major} = 6.6 min , t_{minor} = 7.9 min; ee = 99%.

$[\alpha]_D^{25}$= -44.6 (c =0.40, CH_2Cl_2).

FTIR (neat): υ 3348, 2922, 1583, 1556, 1441, 1406, 1377, 1286, 1241, 1163, 1212, 1080, 1057, 999, 930, 903, 838, 806, 779, 748, 677.

HRMS (CI) Calcd. for $C_{12}H_{19}NOBrSi$ $[M+H]^+$: 300.0419, Found: 300.0424.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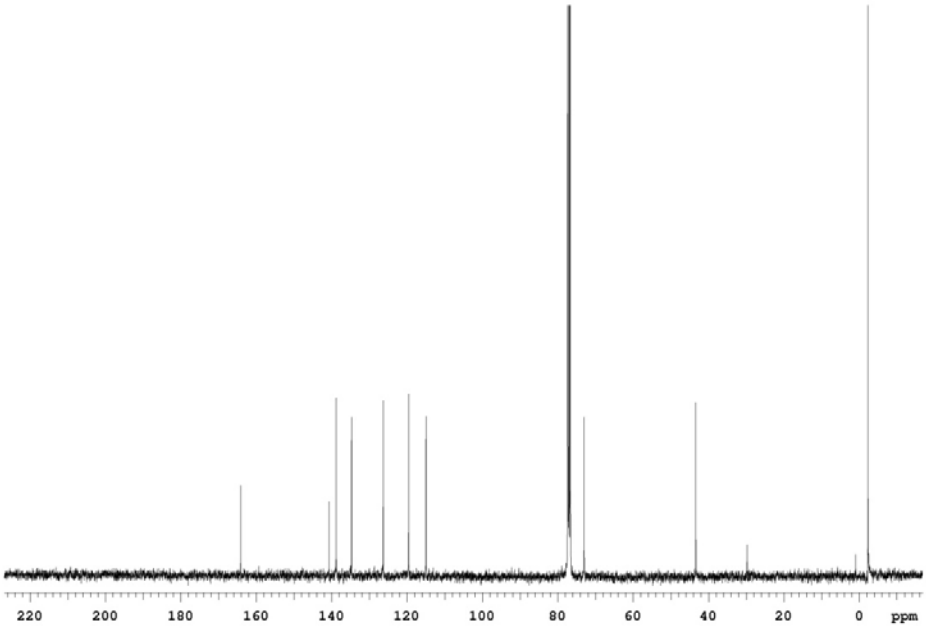
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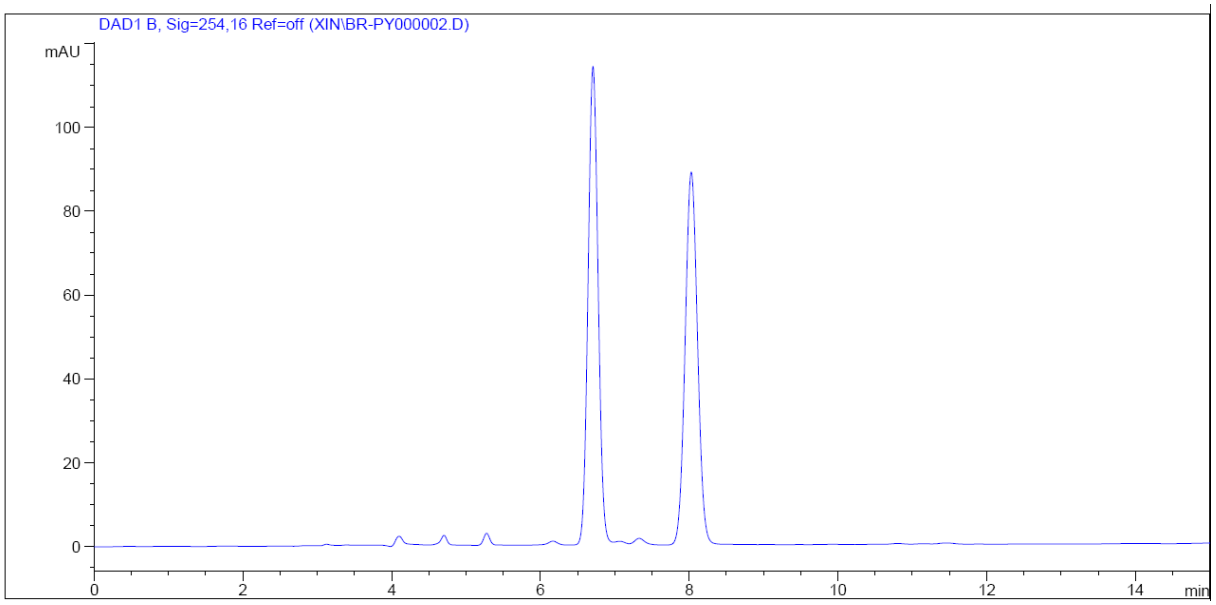
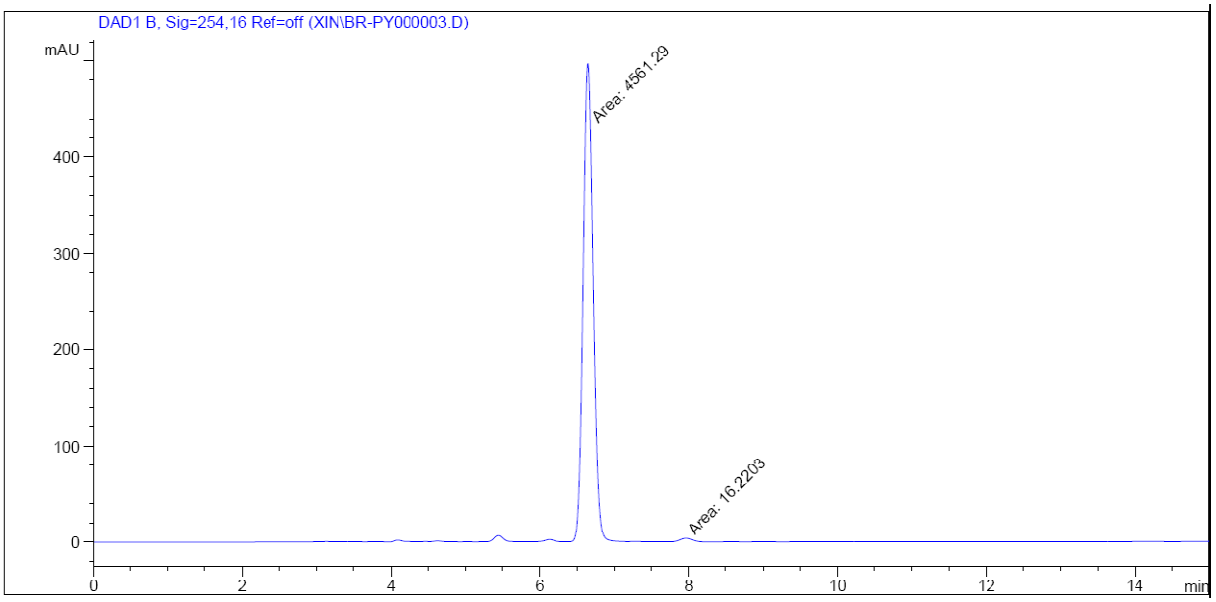
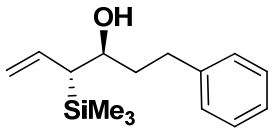


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.703	BB	0.1470	1065.36157	114.00947	50.9372
2	8.025	BB	0.1806	1026.15857	88.95495	49.0628



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.645	MM	0.1532	4561.29199	496.27118	99.6457
2	7.933	MM	0.0710	16.22029	3.80850	0.3543

(3*S*,4*R*)-1-phenyl-4-(trimethylsilyl)hex-5-en-3-ol (2.3a)



An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 3-phenylpropanal **2.4a** (26.8 mg, 0.20 mmol, 100 mol%), *(R)*-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%), isopropanol (24 mg, 0.4 mmol, 200 mol%) and α-(trimethylsilyl)allyl acetate (103 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **2.3a** (34.3 mg, 0.138 mmol) as a colorless oil in 69% yield.

TLC (SiO_2): R_f = 0.3 (ethyl acetate:hexanes, 1:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.26 (m, 2H), 7.20-7.17 (m, 3H), 5.79 (dt, *J* = 17.2, 10.8 Hz, 1H), 5.06 (dd, *J* = 10.4, 2.0 Hz, 1H), 4.95 (dd, *J* = 17.2, 2.0 Hz, 1H), 3.84-3.82 (m, 1H), 2.76-2.63 (m, 2H), 1.84-1.71 (m, 3H), 0.04 (s, 9H).

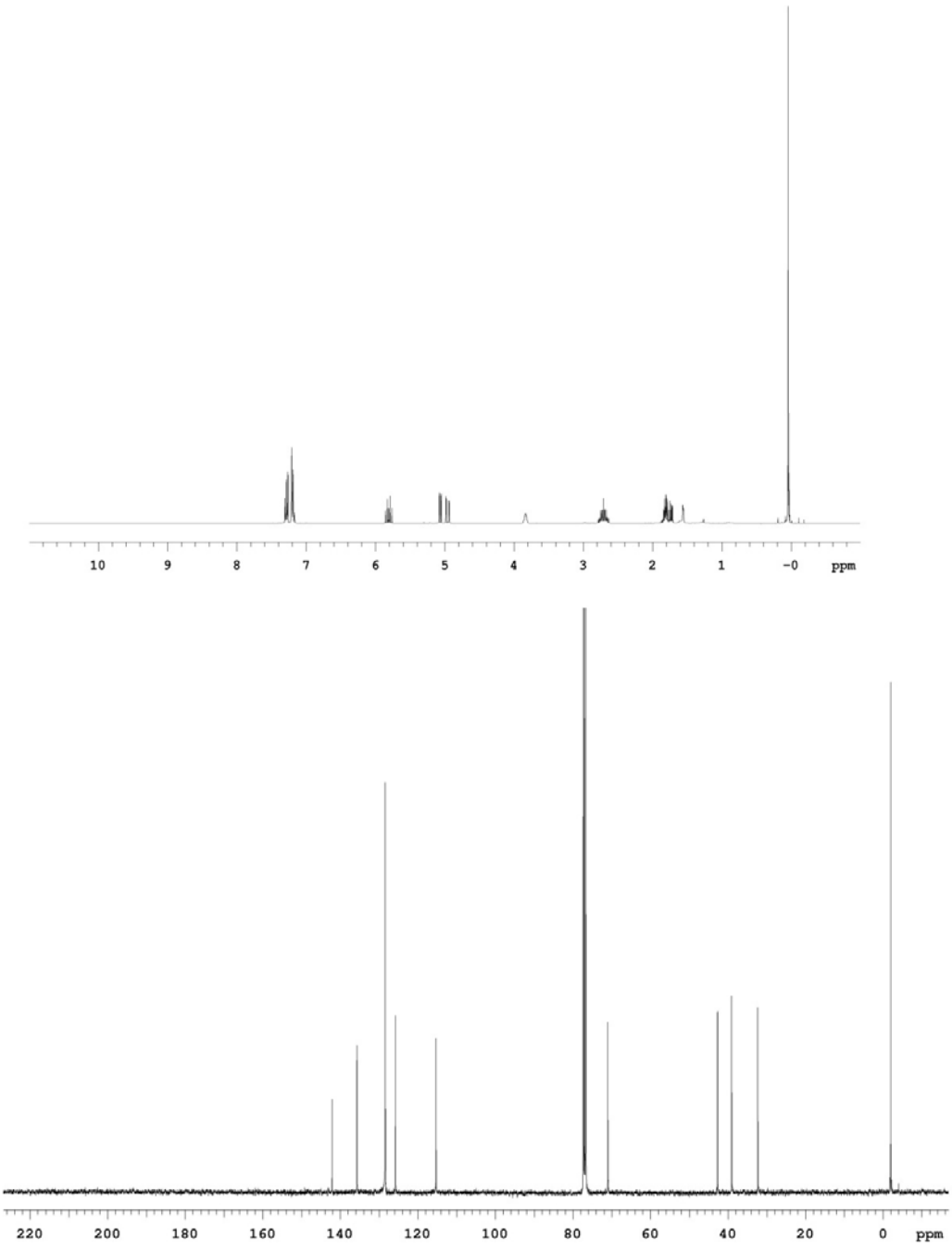
^{13}C NMR (100 MHz, $CDCl_3$): δ 142.1, 135.7, 128.4, 128.3, 125.8, 115.3, 71.0, 42.7, 39.1, 32.3, -2.0.

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 210 nm), t_{major} = 12.1 min, t_{minor} = 16.8 min ; ee = 98%.

$[\alpha]_D^{25}$= +13.3 (c =0.60, CH_2Cl_2).

FTIR (neat): υ 3448, 3027, 2951, 1624, 1603, 1495, 1454, 1414, 1246, 1167, 1098, 1044, 999, 897, 835, 748, 698.

HRMS (CI) Calcd. for $C_{15}H_{23}OSi$ $[M-H]^+$: 247.1518, Found: 247.1520.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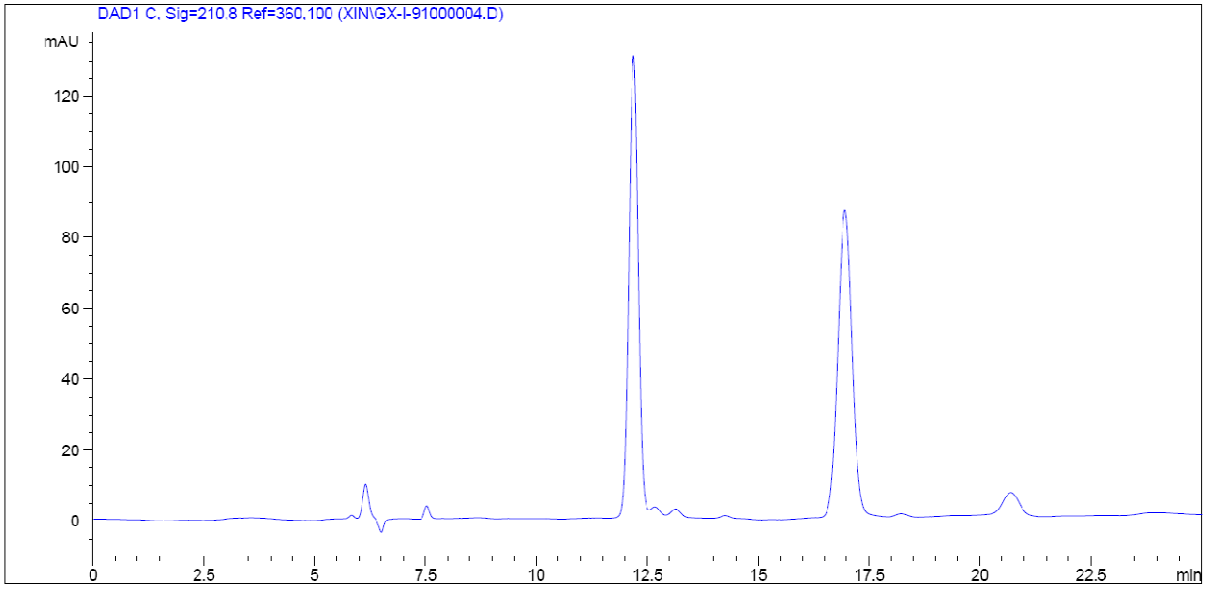

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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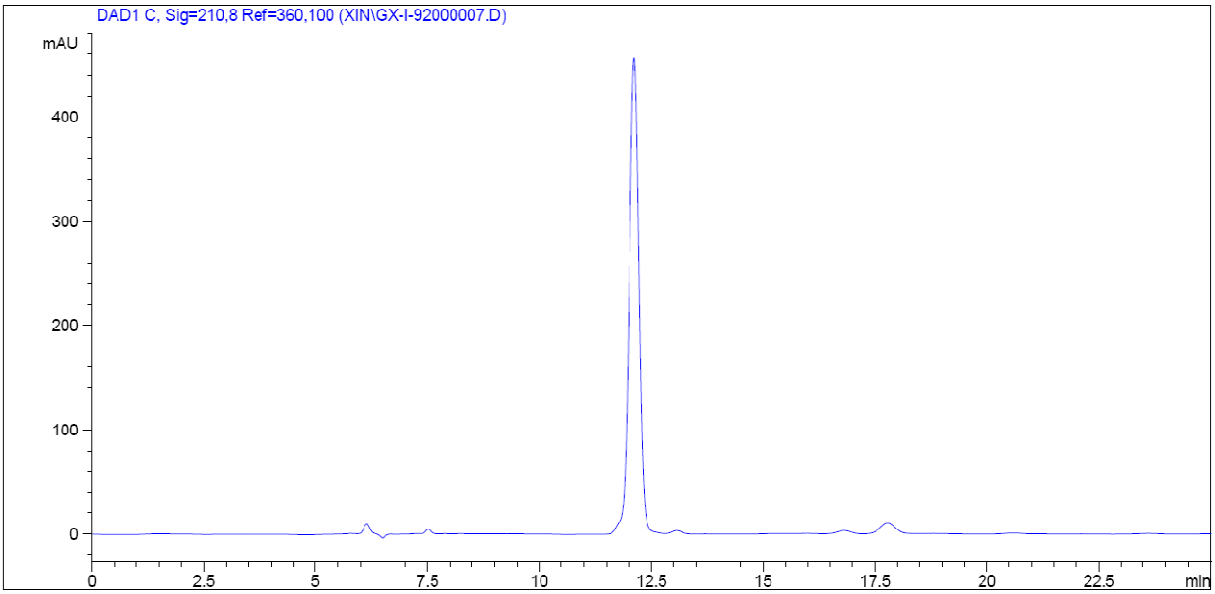
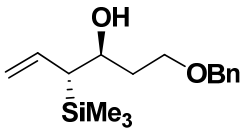
2	16.951	BB	0.3462	1931.14453	86.57128	50.1472



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.112	BB	0.2351	6938.44824	456.97983	99.1868
2	16.806	BB	0.2874	56.88535	2.89344	0.8132

(3*S*,4*R*)-1-(benzyloxy)-4-(trimethylsilyl)hex-5-en-3-ol (2.3g)



An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 3-(benzyloxy)propanal **2.4g** (32.8 mg, 0.20 mmol, 100 mol%), *(R)*-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%), isopropanol (24 mg, 0.4 mmol, 200 mol%) and α-(trimethylsilyl)allyl acetate (103 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **2.3g** (35.1 mg, 0.126 mmol) as a colorless oil in 63% yield (4:1 dr).

TLC (SiO_2): R_f = 0.3 (ethyl acetate:hexanes, 1:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.29 (m, 5H), 5.90 (dt, *J* = 17.2, 10.4 Hz, 1H), 4.99 (dd, *J* = 10.4, 2.4 Hz, 1H), 4.87 (ddd, *J* = 17.2, 2.4, 0.8 Hz, 1H), 4.52 (s, 2H), 4.08-4.01 (m, 1H), 3.72-3.61 (m, 2H), 2.74-2.73 (m, 1H), 1.95-1.85 (m, 1H), 1.65-1.58 (m, 2H), 0.05 (s, 9H).

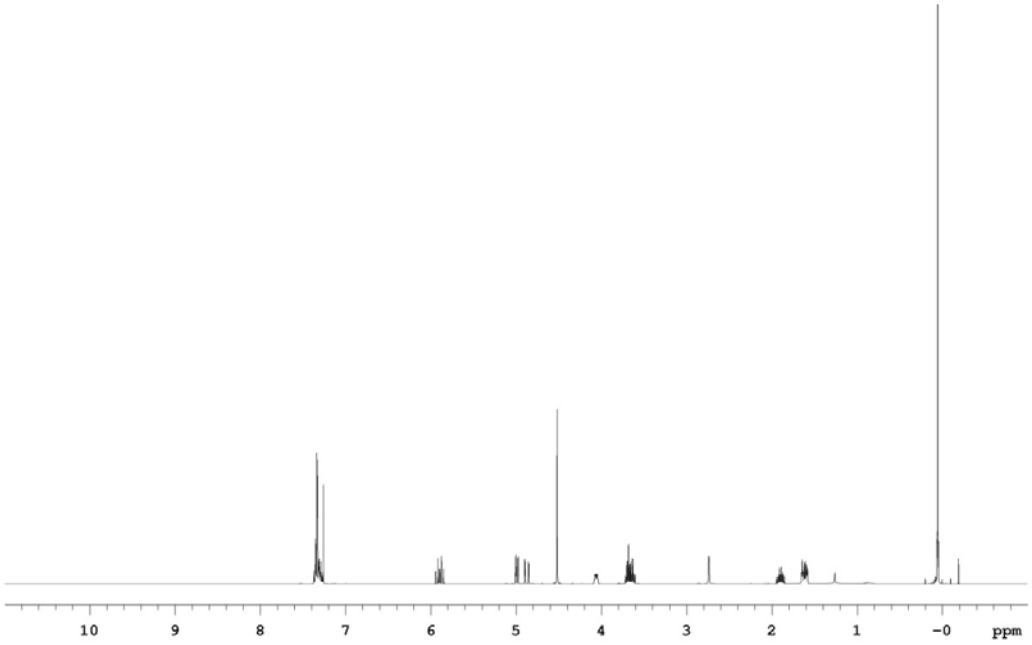
^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 136.1, 128.4, 127.7, 127.6, 114.1, 73.2, 71.3, 69.4, 43.2, 36.8, -2.1.

HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 97.5:2.5, 0.5 mL/min, 210 nm), t_{major} = 11.8 min, t_{minor} = 13.3 min; ee = 98%.

$[\alpha]_D^{25}$= +26.7 (c =0.64, CH_2Cl_2).

FTIR (neat): υ 3511, 2951, 2860, 1623,1496, 1454, 1414, 1362, 1244, 1205, 1088, 1027, 1004, 896, 835, 780, 733, 696.

HRMS (CI) Calcd. for $C_{16}H_{25}O_2Si$ $[M-H]^+$: 277.1624, Found: 277.1627.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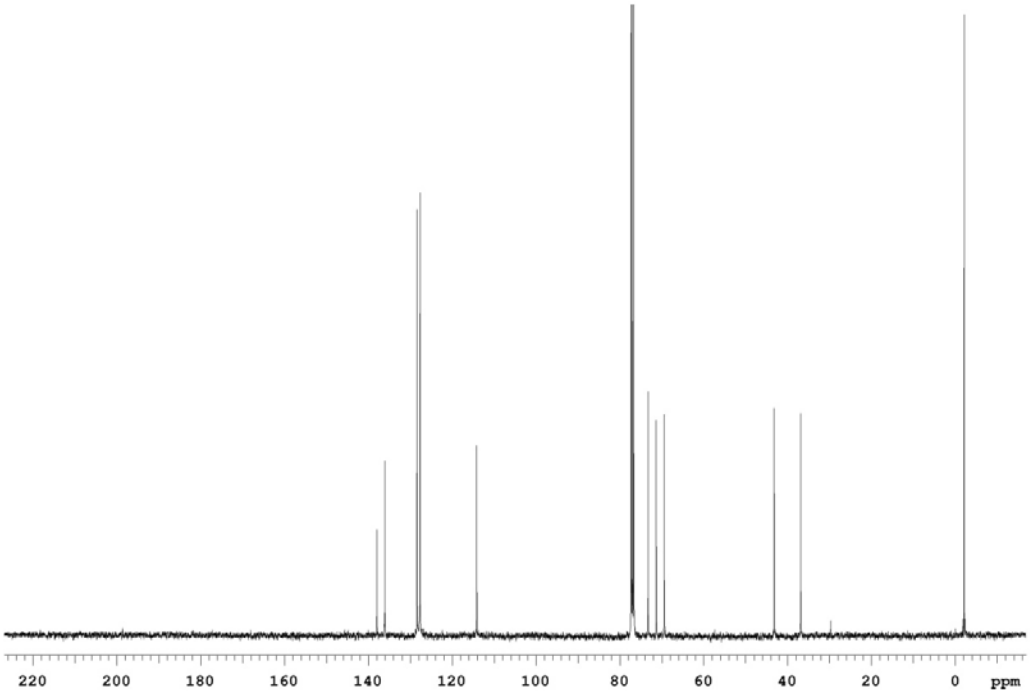
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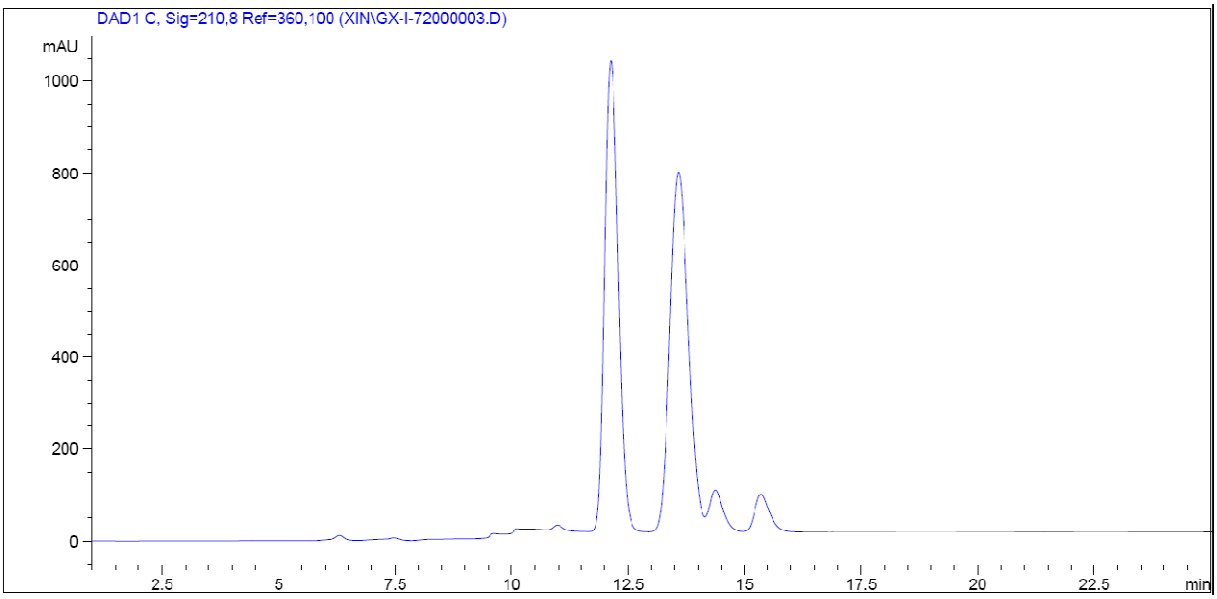
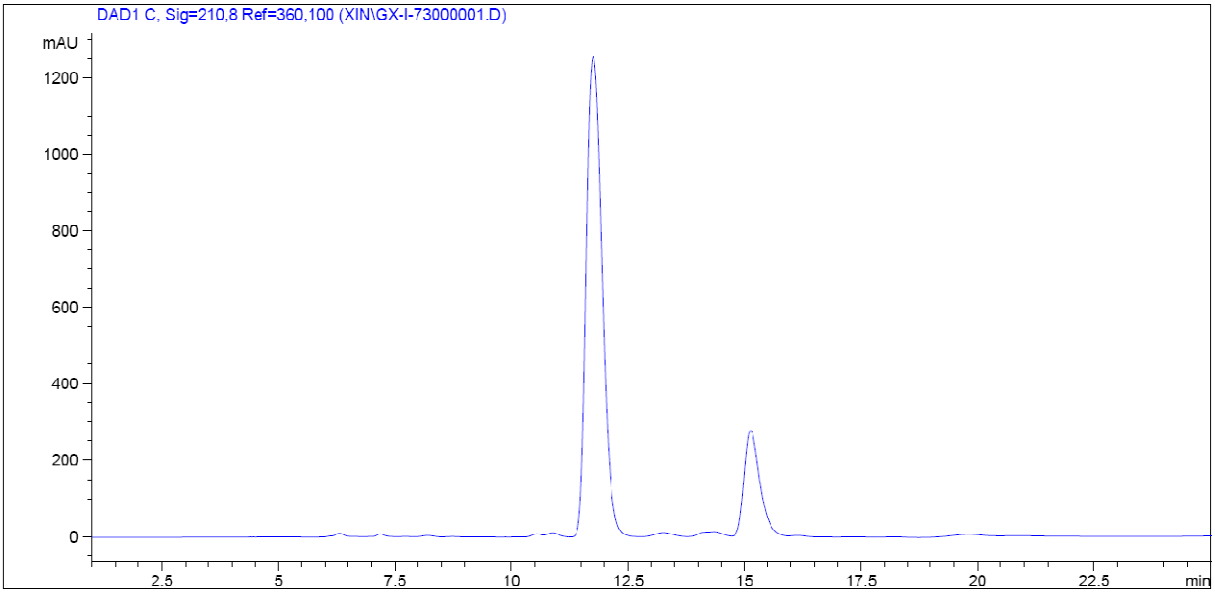
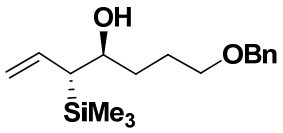


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.126	BB	0.3251	2.09667e4	1023.14630	45.4032
2	13.576	BV	0.4364	2.15672e4	780.54895	46.7036
3	14.366	VV	0.3143	1863.62976	89.71630	4.0357
4	15.347	VB	0.3376	1781.34241	80.69200	3.8575



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.751	VB	0.3780	2.98928e4	1254.47681	98.9642
2	13.258	BV	0.4317	312.87262	10.87367	1.0358

(3*R*,4*S*)-7-(benzyloxy)-3-(trimethylsilyl)hept-1-en-4-ol (2.3h)



An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with). 4-(benzyloxy)butana **2.4h** (35.6 mg, 0.20 mmol, 100 mol%), *(R)*-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%), isopropanol (24 mg, 0.4 mmol, 200 mol%) and α-(trimethylsilyl)allyl acetate (103 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **2.3h** (40.4 mg, 0.138 mmol) as a colorless oil in 69% yield.

TLC (SiO_2): R_f = 0.4 (ethyl acetate:hexanes, 1:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 5.83 (dt, *J* = 16.8, 10.4 Hz, 1H), 5.02 (dd, *J* = 10.4, 2.4 Hz, 1H), 4.91 (ddd, *J* = 16.8, 2.4, 0.8 Hz, 1H), 4.52 (m, 2H), 3.86-3.80 (m, 1H), 3.52-3.48 (m, 2H), 2.13 (d, *J* = 4.0 Hz, 1H), 1.75-1.49 (m, 5H), 0.04 (s, 9H).

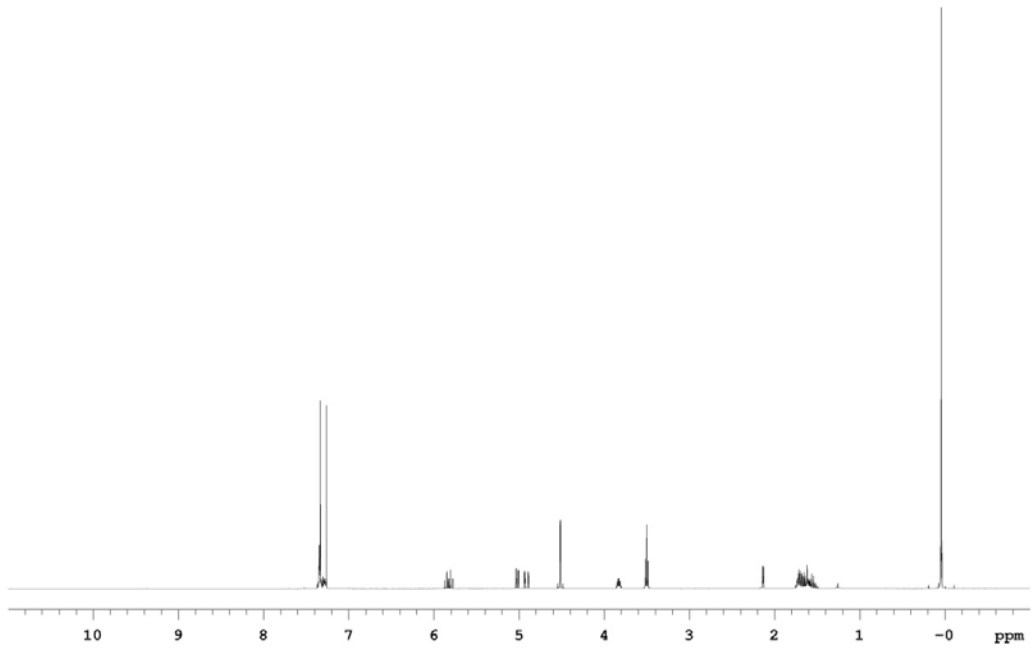
^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 136.0, 128.4, 127.6, 127.5, 114.7, 72.9, 71.2, 70.4, 42.8, 34.5, 26.4, -2.1.

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 210 nm), t_{minor} = 10.9 min, t_{major} = 12.2 min; ee = 98%.

$[\alpha]_D^{25}$= +41.2 (c =0.63, CH_2Cl_2).

FTIR (neat): υ 3448, 2950, 2857, 1624, 1496, 1454, 1362, 1244, 1204, 1097, 1028, 950, 895, 835, 782, 734, 696.

HRMS (CI) Calcd. for $C_{17}H_{27}O_2Si$ $[M-H]^+$: 291.1780, Found: 292.1781.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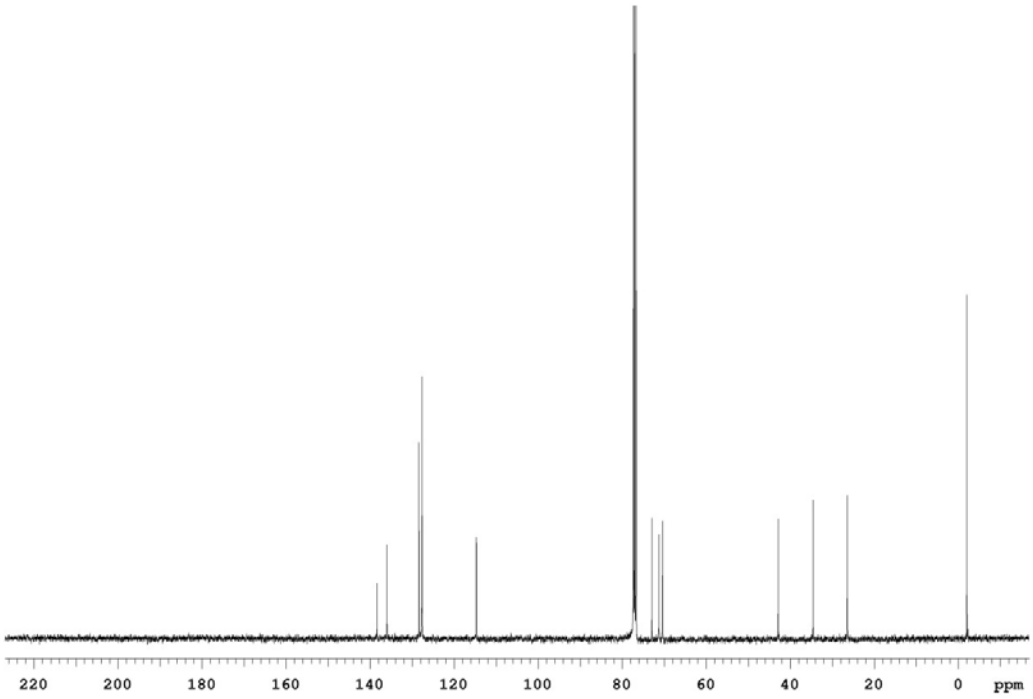
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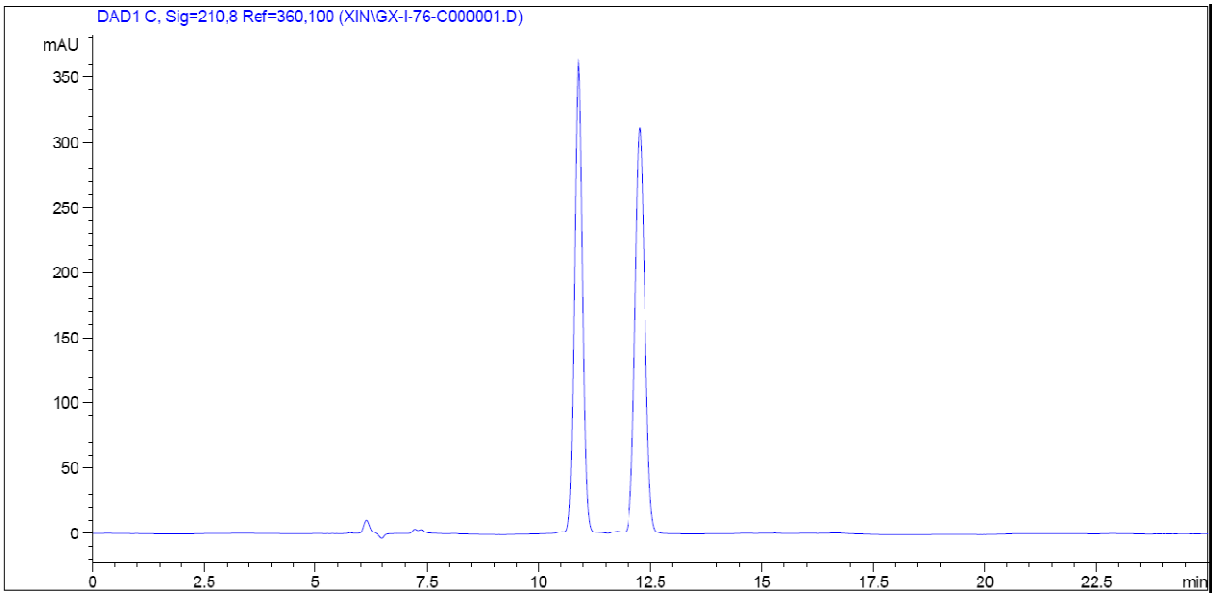
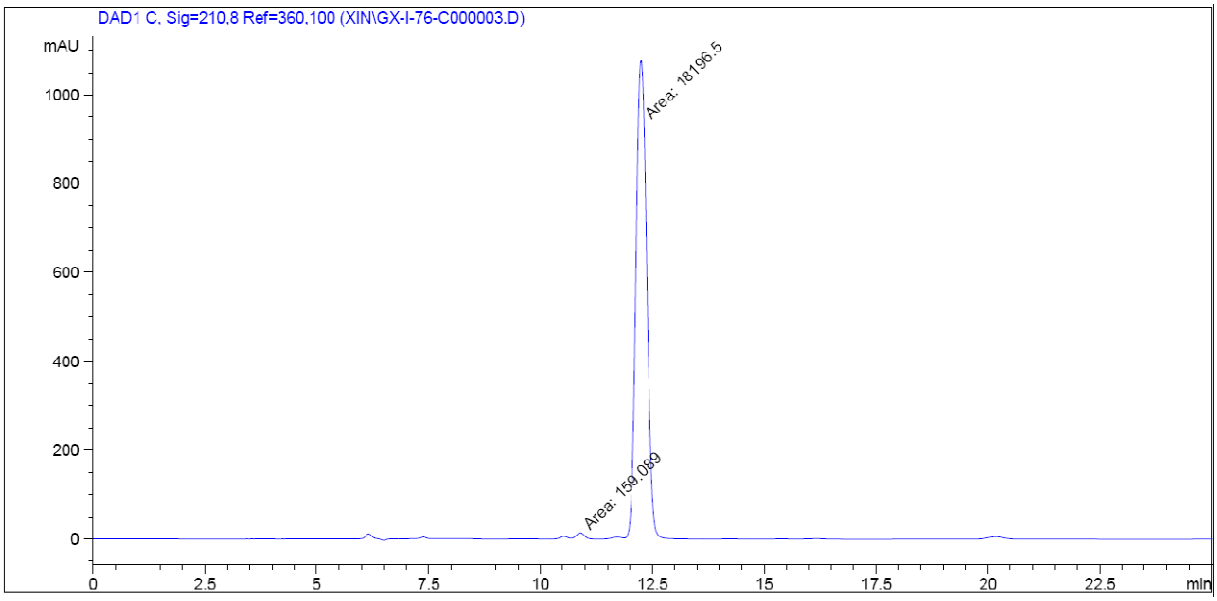
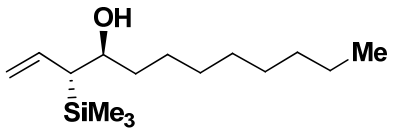


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.888	BB	0.2039	4741.20605	364.03851	49.9308
2	12.265	VB	0.2382	4754.34570	311.30685	50.0692



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.884	MM	0.2090	159.08887	12.68839	0.8667
2	12.245	MM	0.2799	1.81965e4	1083.52197	99.1333

(3*R*,4*S*)-3-(trimethylsilyl)dodec-1-en-4-ol (2.3c)



An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with nonanal **2.4c** (28.4 mg, 0.20 mmol, 100 mol%), *(R)*-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%), isopropanol (24 mg, 0.4 mmol, 200 mol%) and α-(trimethylsilyl)allyl acetate (103 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **2.3c** (36.9 mg, 0.144 mmol) as a colorless oil in 72% yield.

TLC (SiO_2): R_f = 0.4 (ethyl acetate:hexanes, 1:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79 (dt, *J* = 17.2, 10.4 Hz, 1H), 5.03 (d, *J* = 10.4 Hz, 1H), 4.92 (d, *J* = 17.2 Hz, 1H), 3.84-3.74 (m, 1H), 1.69-1.65 (m, 1H), 1.49-1.26 (m, 15H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.04 (s, 9H).

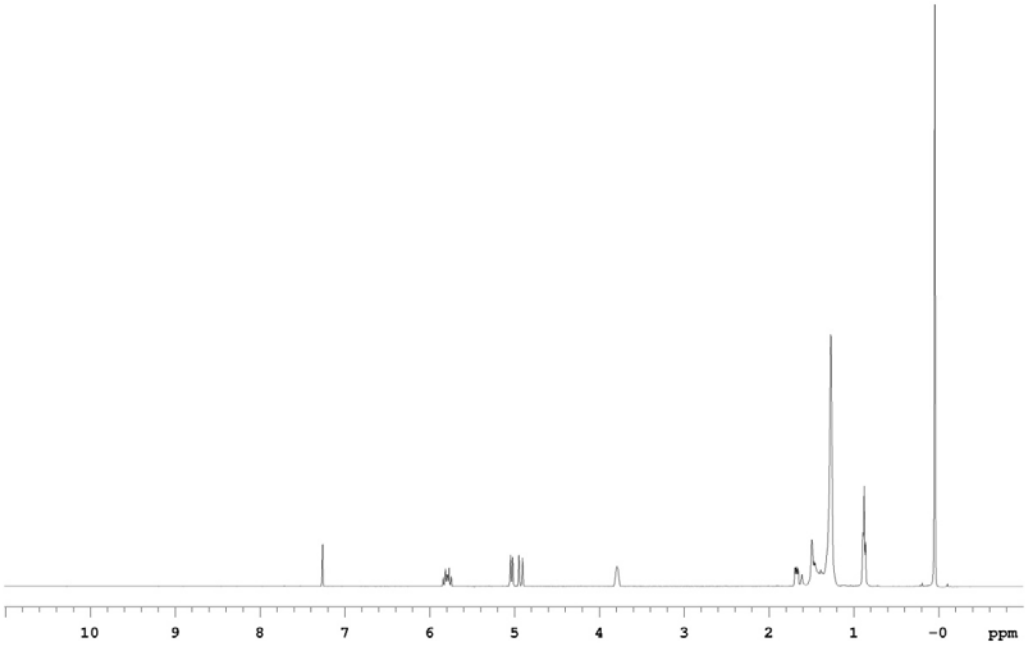
^{13}C NMR (100 MHz, $CDCl_3$): δ 135.9, 115.0, 71.5, 42.6, 37.3, 31.9, 29.6, 29.3, 25.8, 22.7, 14.1, -2.0.

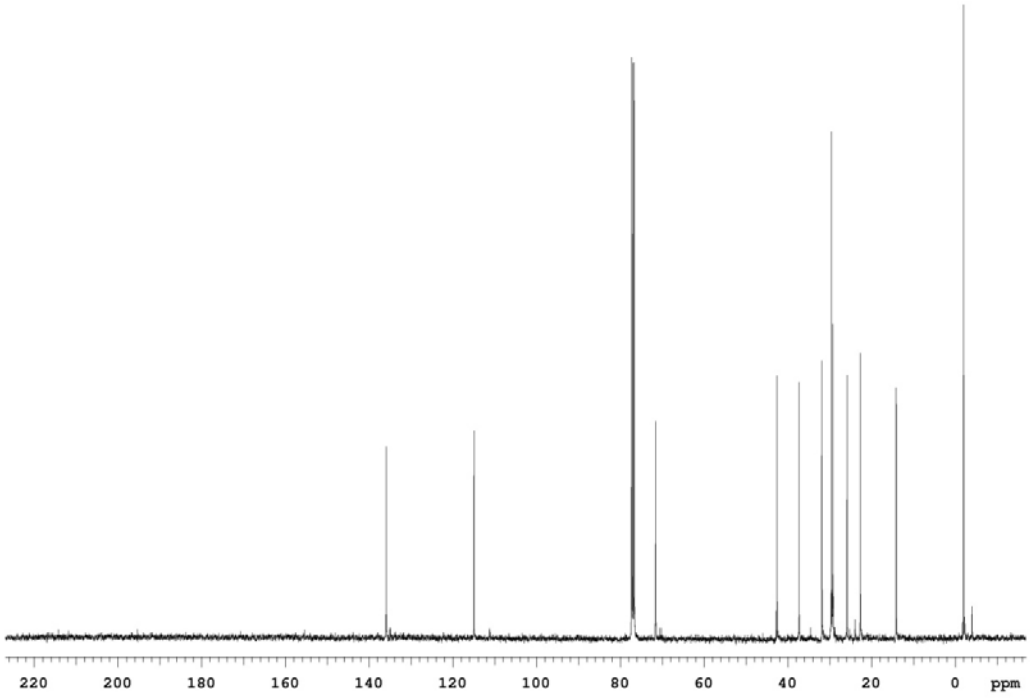
HPLC: Enantiomeric excess was determined by HPLC analysis of the 3,5-nitrobenzoate derivative of the product (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 254 nm), t_{minor} = 10.7 min, t_{major} = 11.3 min; ee = 90%.

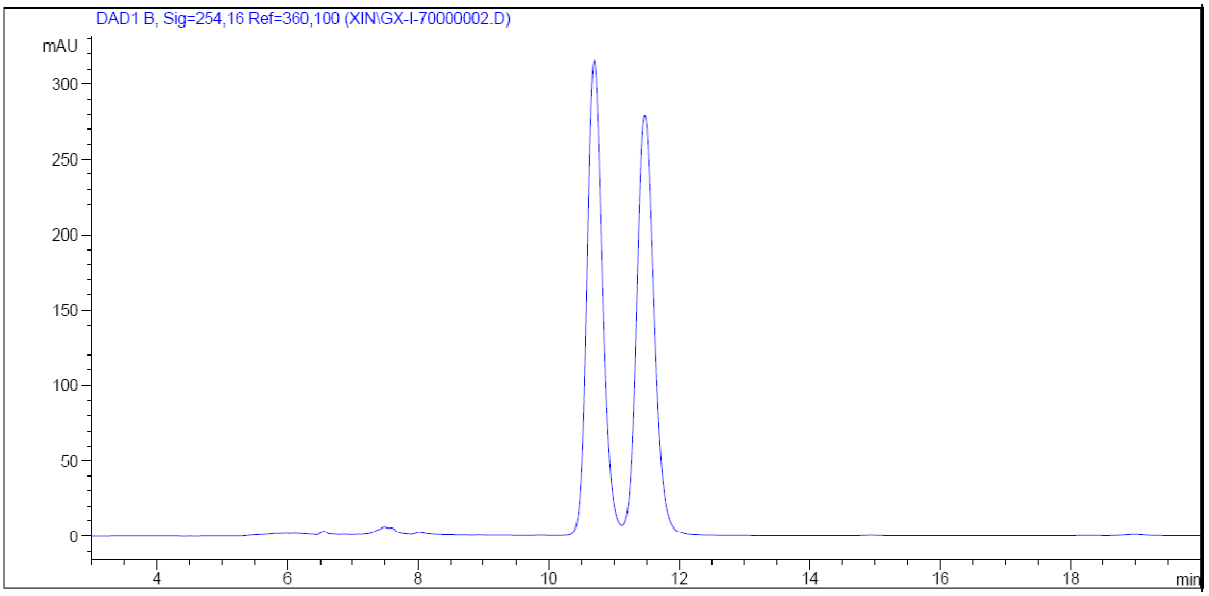
$[\alpha]_D^{25}$= +21.2 (c =0.57, CH_2Cl_2).

FTIR (neat): υ 3463, 2955, 2924, 2854, 1716, 1624, 1465, 1378, 1246, 1167, 1049, 1004, 895, 836, 750, 723, 690.

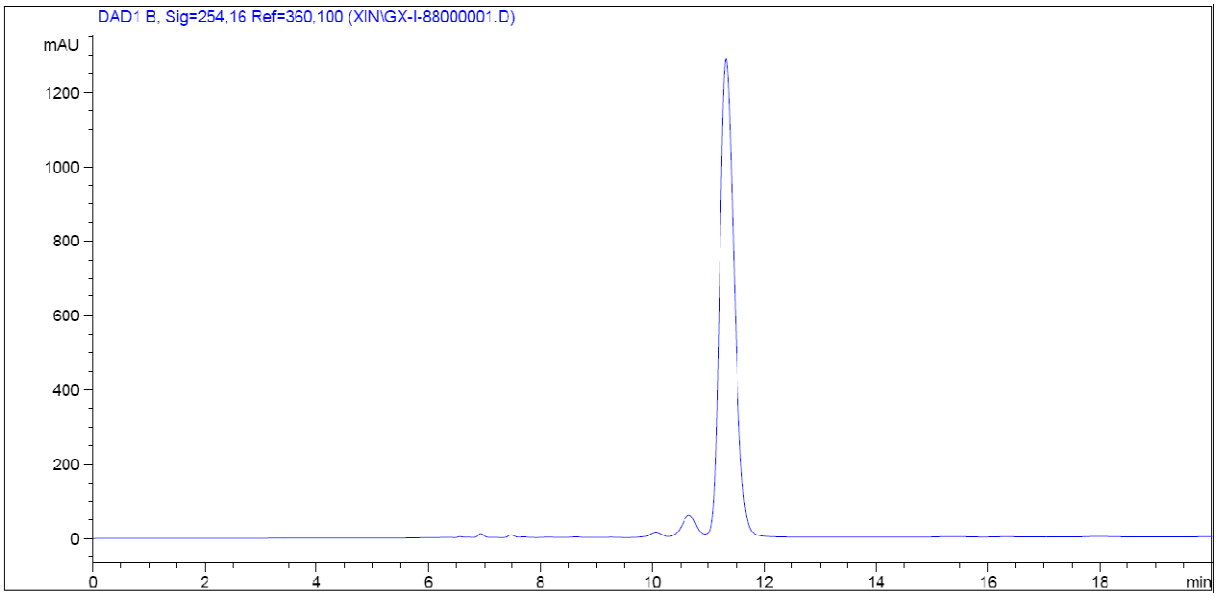
HRMS (CI) Calcd. for $C_{15}H_{31}OSi$ $[M-H]^+$: 255.2144, Found: 255.2132.


10
9
8
7
6
5
4
3
2
1
-0
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm

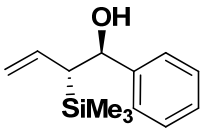


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.696	BV	0.2546	5203.19336	315.17252	50.3147
2	11.472	VB	0.2851	5138.10547	278.73831	49.6853



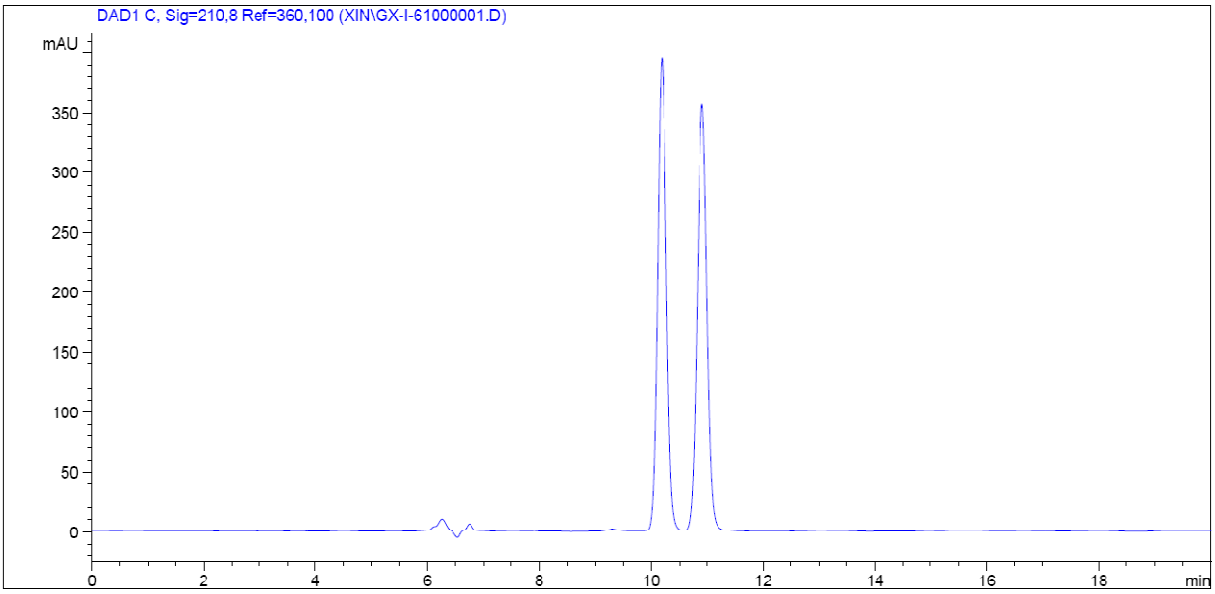
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.653	VV	0.2754	1097.22620	60.55373	4.4990
2	11.315	VB	0.2831	2.32909e4	1286.94128	95.5010

(1*S*,2*R*)-1-phenyl-2-(trimethylsilyl)but-3-en-1-ol (2.2f)

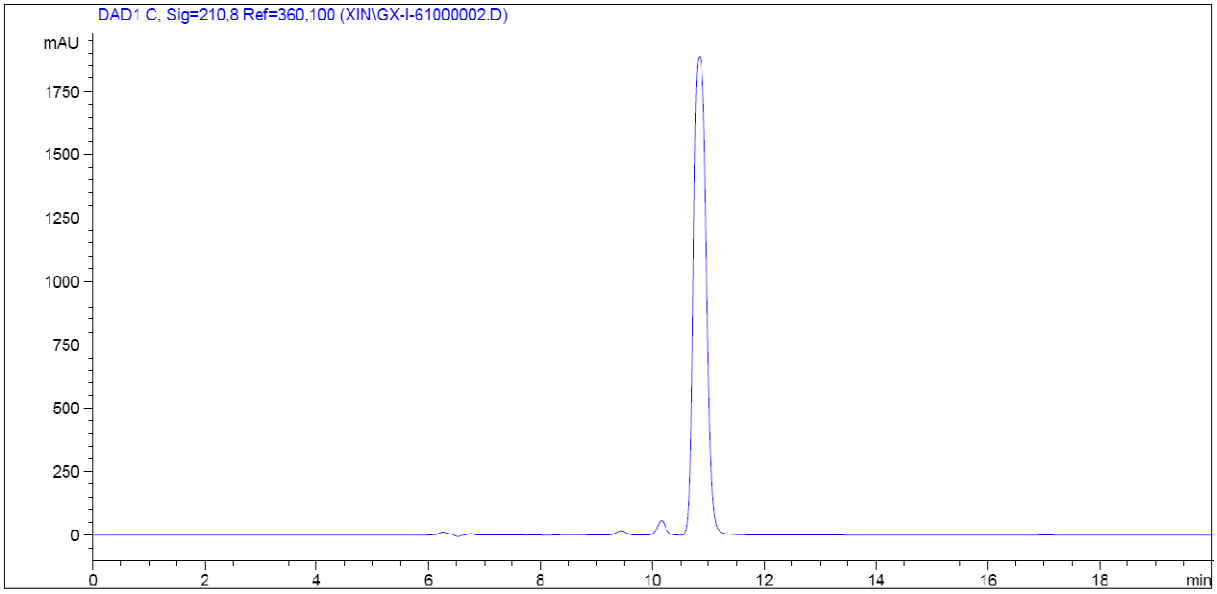


An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with benzyl alcohol **2.2f** (21.6 mg, 0.20 mmol, 100 mol%), *(R)*-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%) and α-(trimethylsilyl)allyl acetate (103 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 to 1:10 with 0.1% TEA) provided **2.3f** (30.4 mg, 0.138 mmol) as a colorless oil in 69% yield.

HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 210 nm), t_{minor} = 10.2 min, t_{major} = 10.8 min; ee = 96%.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.189	BV	0.1672	4244.84766	395.51974	49.7522
2	10.904	VB	0.1863	4287.12988	356.53409	50.2478

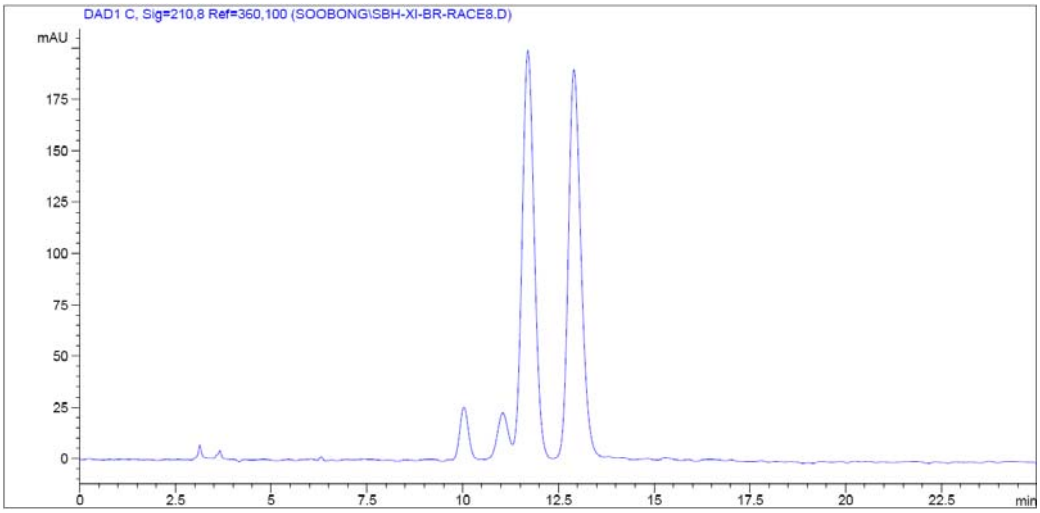


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.160	BV	0.1663	612.62158	57.48452	2.0155
2	10.834	VB	0.2543	2.97835e4	1885.13000	97.9845

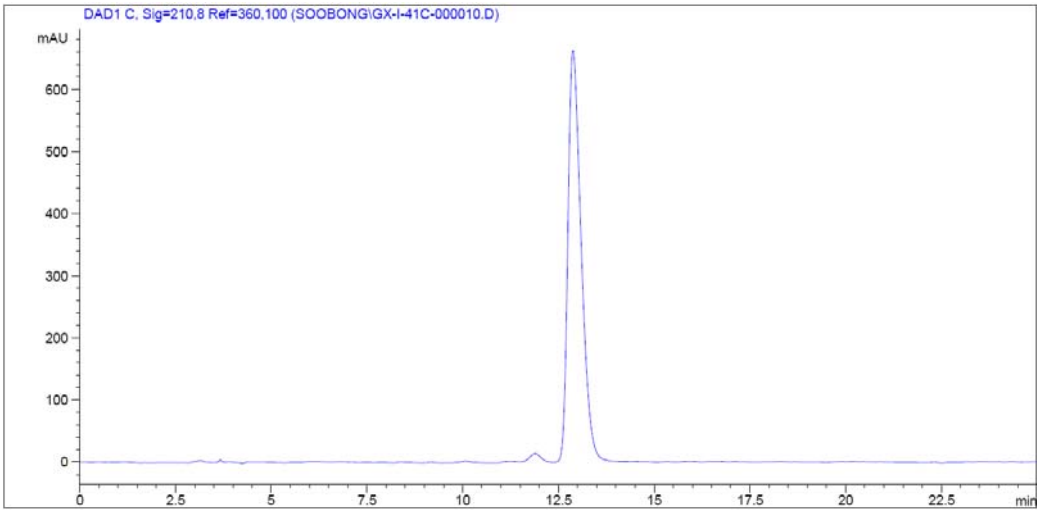
(1*S*,2*R*)-1-(4-bromophenyl)-2-(trimethylsilyl)but-3-en-1-ol (2.3d)

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 4-bromobenzyl alcohol **2.2d** (37.4 mg, 0.20 mmol, 100 mol%), *(R)*-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%) and α-(trimethylsilyl)allyl acetate (103 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **2.3d** (43.1 mg, 0.144 mmol) as a colorless oil in 72% yield.

HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 210 nm), t_{minor} = 11.9 min, t_{major} = 12.9 min; ee = 96%.

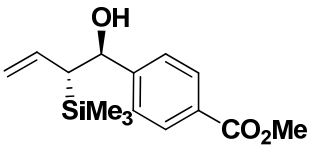


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.030	VB	0.2658	460.92273	26.64501	4.6287
2	11.043	BV	0.3217	493.99435	23.84700	4.9608
3	11.699	VV	0.3408	4482.47461	200.55130	45.0140
4	12.903	VB	0.3555	4520.55859	191.44574	45.3965



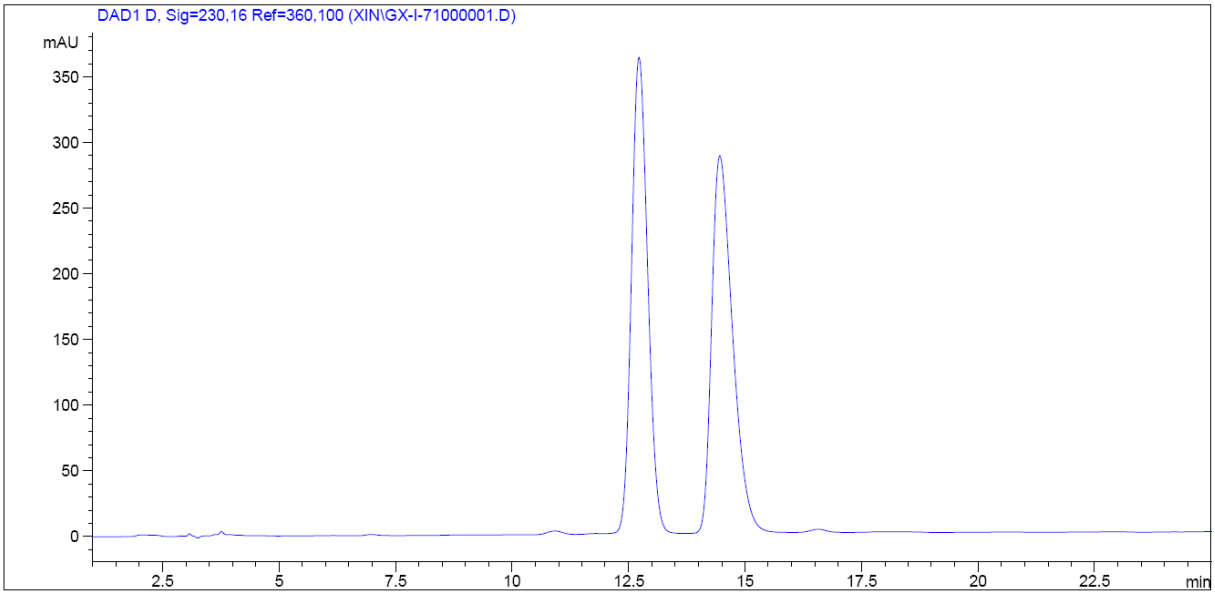
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.890	VV	0.3701	362.59784	14.99740	2.1903
2	12.879	VV	0.3724	1.61922e4	664.24304	97.8097

methyl 4-((1*S*,2*R*)-1-hydroxy-2-(trimethylsilyl)but-3-enyl)benzoate (2.3e)

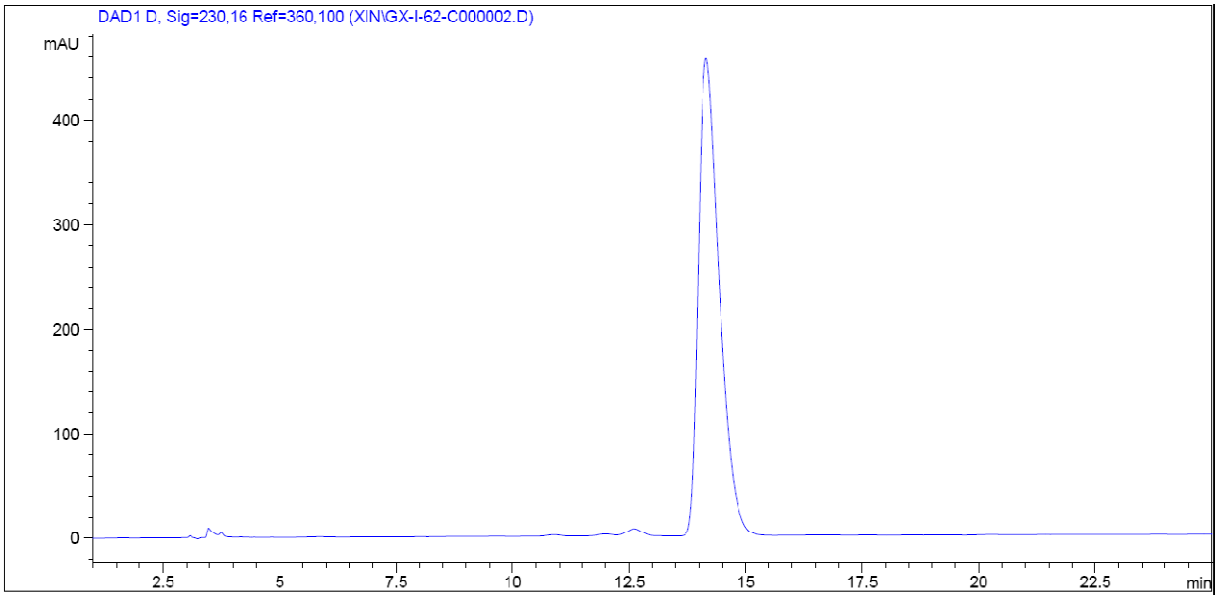


An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with methyl 4-(hydroxymethyl)benzoate **2.2e** (33.2 mg, 0.20 mmol, 100 mol%), *(R)*-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%) and α-(trimethylsilyl)allyl acetate (103 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **2.3e** (41.8 mg, 0.150 mmol) as a colorless oil in 75% yield.

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 230 nm), t_{minor} = 12.6 min, t_{major} = 14.1 min; ee = 98%.

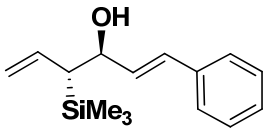


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.720	BB	0.3757	8754.31348	362.51440	49.4581
2	14.454	BB	0.4775	8946.14551	287.11798	50.5419



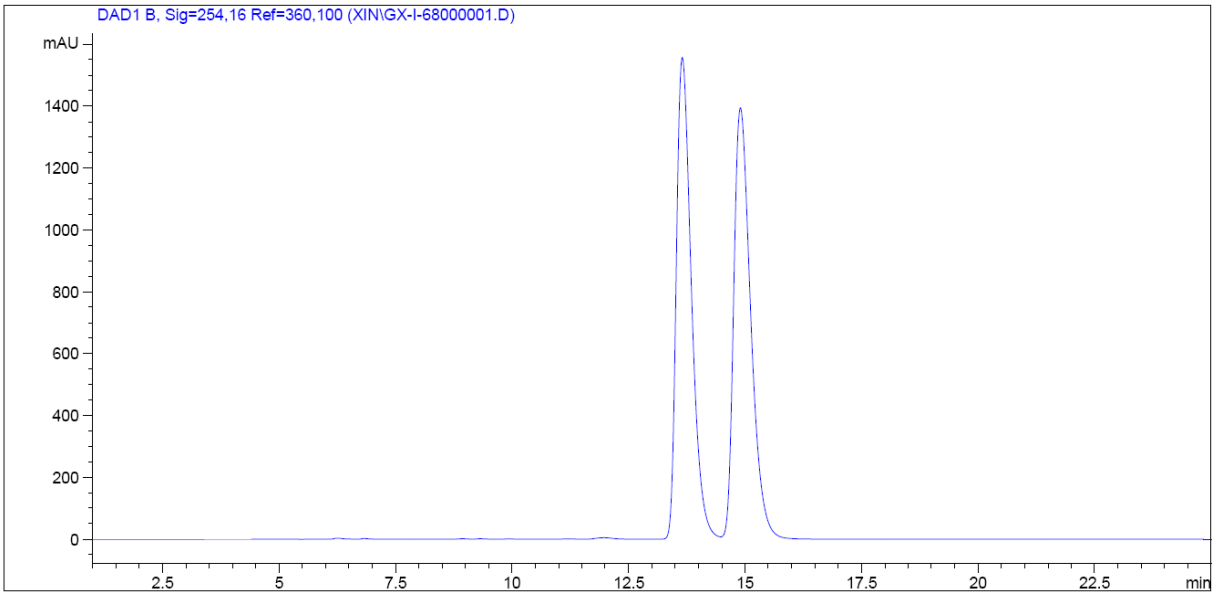
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.606	VB	0.3674	167.55223	7.09887	1.1665
2	14.147	BB	0.4749	1.41967e4	456.36560	98.8335

(3*S*,4*R*,*E*)-1-phenyl-4-(trimethylsilyl)hexa-1,5-dien-3-ol (2.3b)

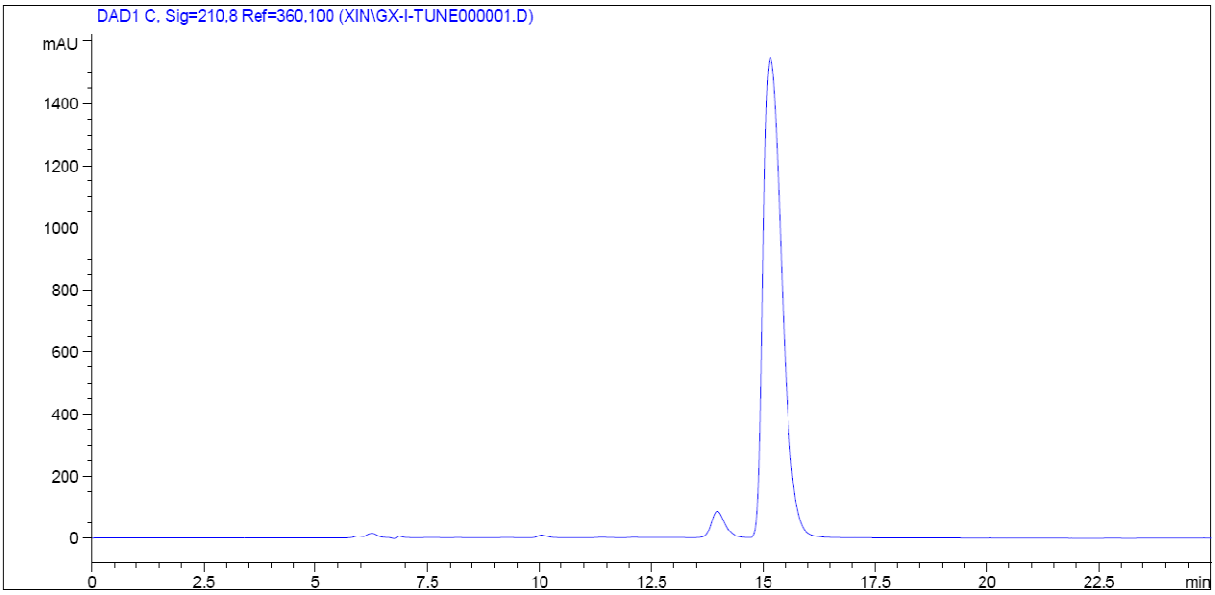


An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with cinnamyl alcohol **2.2b** (26.8 mg, 0.20 mmol, 100 mol%), ***(R)*-C3-TUNEPHOS** (10.2 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%) and α-(trimethylsilyl)allyl acetate (103 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **2.3b** (34.5 mg, 0.140 mmol) as a colorless oil in 70% yield.

HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 210 nm), t_{minor} = 14.0 min, t_{major} = 15.2 min; ee = 92%.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.650	BV	0.3460	3.49861e4	1557.74707	49.7498
2	14.898	VB	0.3875	3.53381e4	1395.15076	50.2502

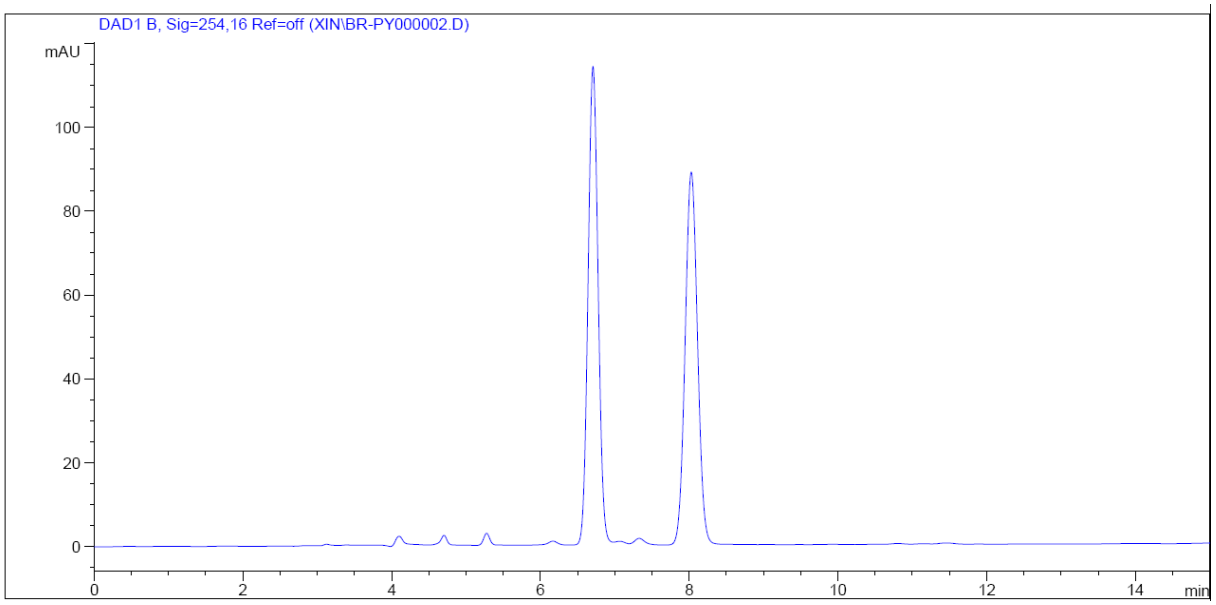


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.971	BV	0.3294	1815.07458	84.21894	3.8860
2	15.155	VB	0.4636	4.48926e4	1542.22046	96.1140

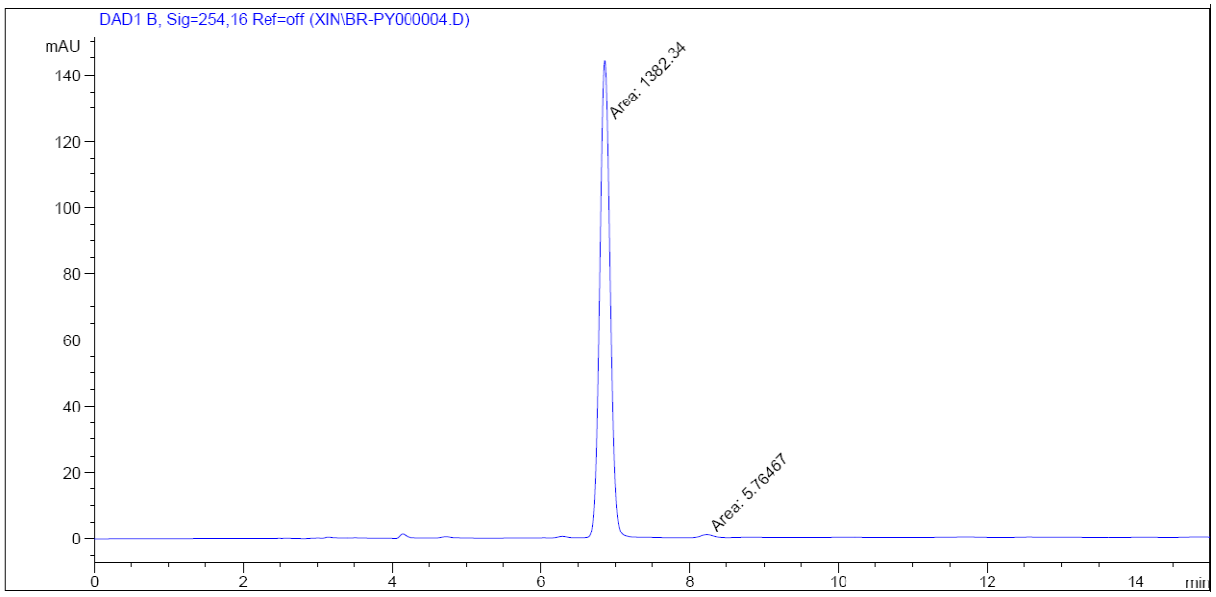
(1*S*,2*R*)-1-(6-bromopyridin-2-yl)-2-(trimethylsilyl)but-3-en-1-ol (2.3i)

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with (6-bromopyridin-2-yl)methanol **2.2i** (37.6 mg, 0.20 mmol, 100 mol%), *(R)*-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%) and α-(trimethylsilyl)allyl acetate (103 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **2.3i** (34.8 mg, 0.116 mmol) as a colorless oil in 58% yield.

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 98:2, 1.0 mL/min, 254 nm), t_{major} = 6.9 min , t_{minor} = 8.2 min; ee = 99%.

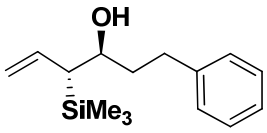


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.703	BB	0.1470	1065.36157	114.00947	50.9372
2	8.025	BB	0.1806	1026.15857	88.95495	49.0628



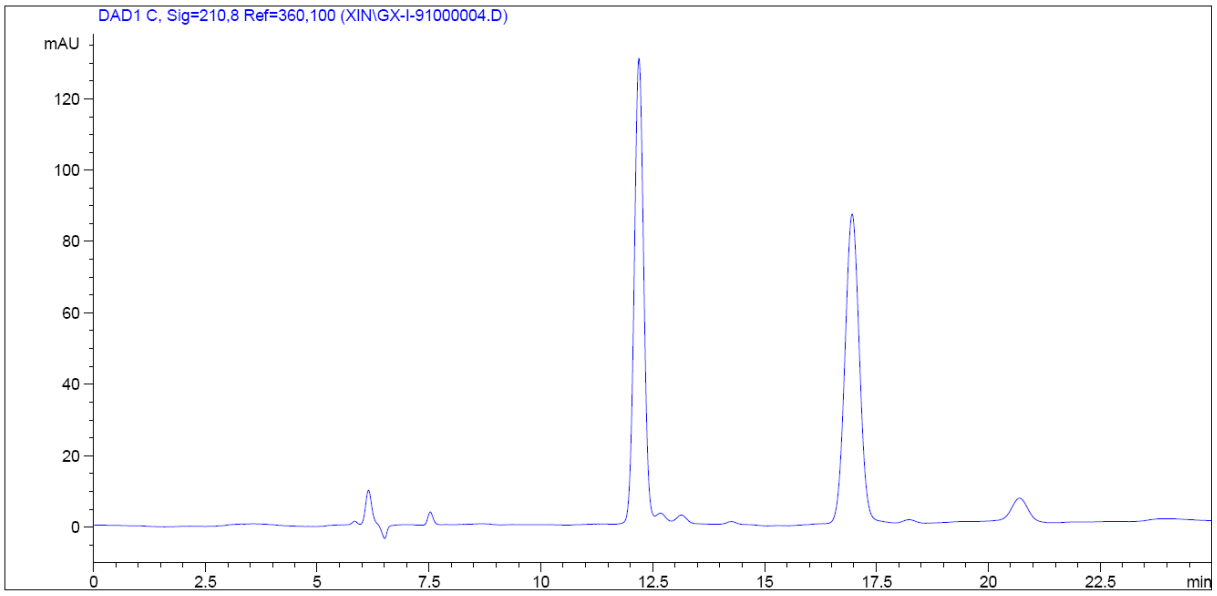
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.856	MM	0.1593	1382.34070	144.59540	99.5847
2	8.236	MM	0.1208	5.76467	7.95557e-1	0.4153

(3*S*,4*R*)-1-phenyl-4-(trimethylsilyl)hex-5-en-3-ol (2.3a)

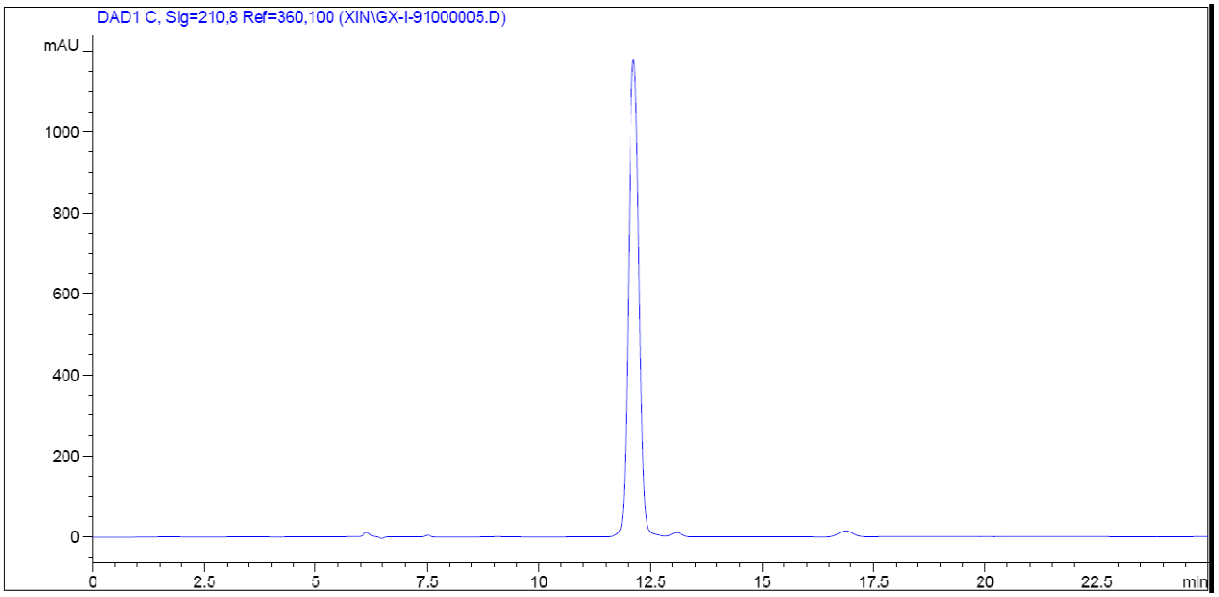


An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 3-phenylpropan-1-ol **2.2a** (27.2 mg, 0.20 mmol, 100 mol%), *(R)*-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%) and α-(trimethylsilyl)allyl acetate (103 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **2.3a** (32.3 mg, 0.130 mmol) as a colorless oil in 65% yield.

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 210 nm), t_{major} = 12.1 min, t_{minor} = 16.9 min ; ee = 97%.

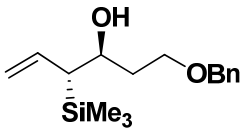


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.186	BV	0.2295	1919.80676	130.59860	49.8528
2	16.951	BB	0.3462	1931.14453	86.57128	50.1472



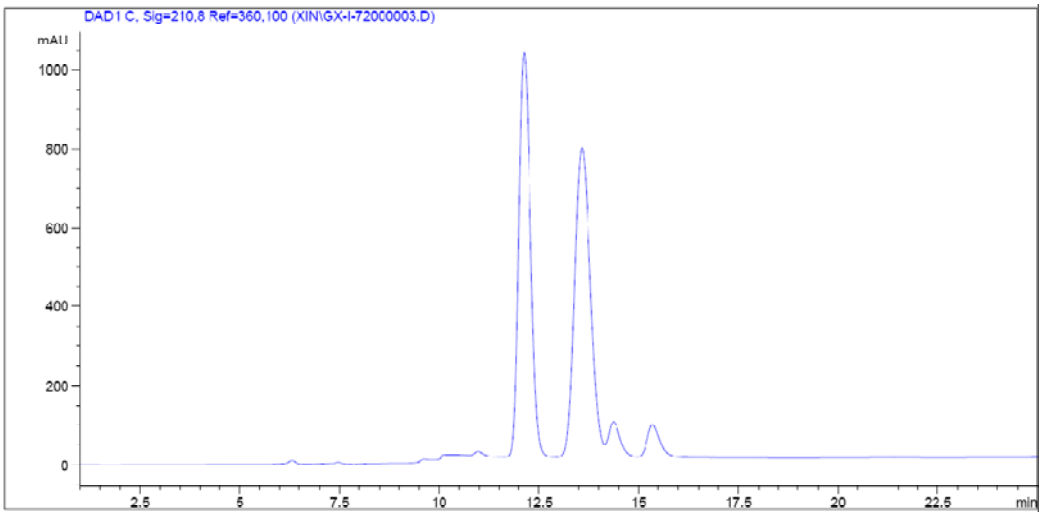
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.118	BB	0.2608	1.92732e4	1178.34497	98.4124
2	16.880	BB	0.3391	310.91425	14.21759	1.5876

(3*S*,4*R*)-1-(benzyloxy)-4-(trimethylsilyl)hex-5-en-3-ol (2.3g)

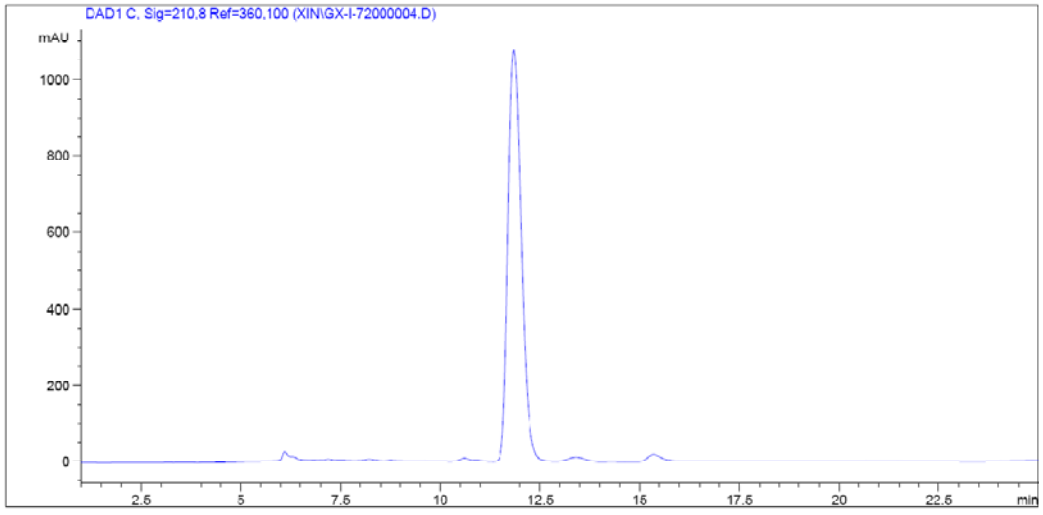


An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 3-(benzyloxy)propan-1-ol **2.2g** (33.2 mg, 0.20 mmol, 100 mol%), *(R)*-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%) and α-(trimethylsilyl)allyl acetate (103 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **2.3g** (34.0 mg, 0.122 mmol) as a colorless oil in 61% yield.

HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 97.5:2.5, 0.5 mL/min, 210 nm), t_{major} = 11.8 min, t_{minor} = 13.4 min; ee = 97%.

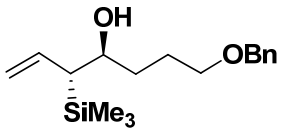


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.126	BB	0.3251	2.09667e4	1023.14630	45.4032
2	13.576	BV	0.4364	2.15672e4	780.54895	46.7036
3	14.366	VV	0.3143	1863.62976	89.71630	4.0357
4	15.347	VB	0.3376	1781.34241	80.69200	3.8575



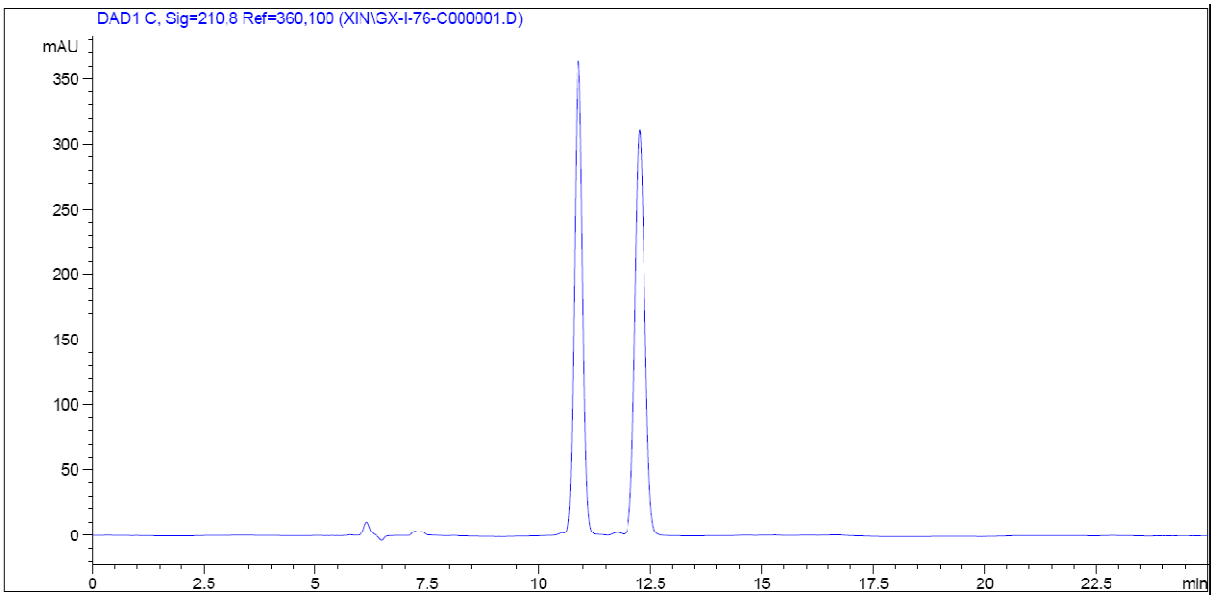
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.842	BB	0.3645	2.49637e4	1076.54944	98.6928
2	13.396	BB	0.4327	330.63715	11.95321	1.3072

(3*R*,4*S*)-7-(benzyloxy)-3-(trimethylsilyl)hept-1-en-4-ol (2.3h)

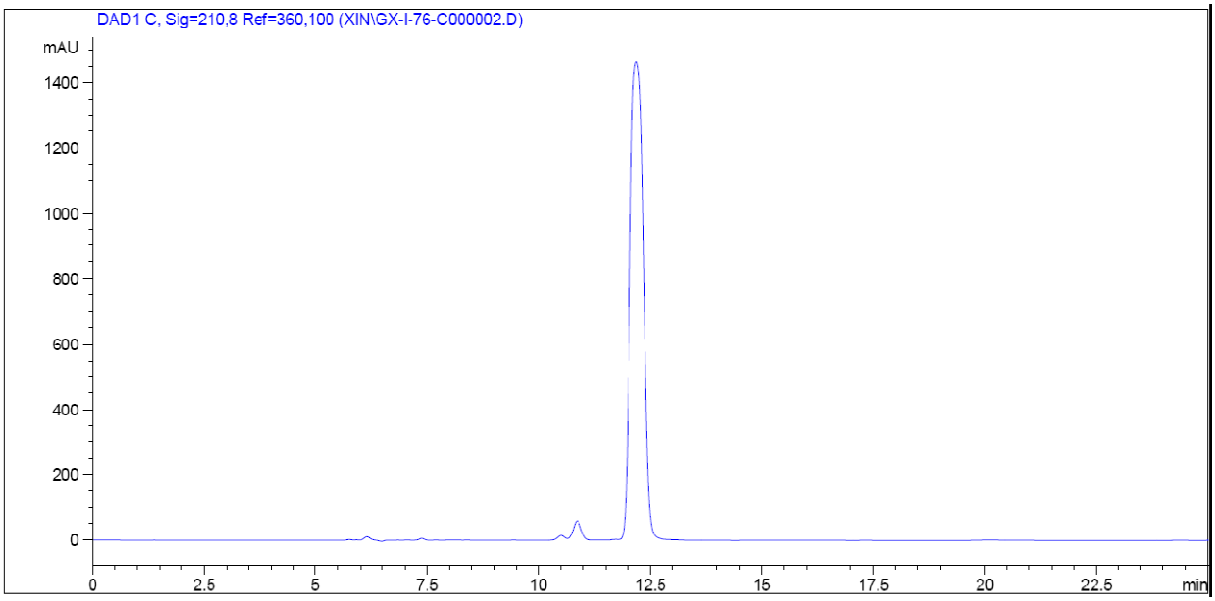


An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with 4-(benzyloxy)butan-1-ol **2.2h** (36.0 mg, 0.20 mmol, 100 mol%), *(R)*-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%) and α-(trimethylsilyl)allyl acetate (103 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **2.3h** (40.4 mg, 0.138 mmol) as a colorless oil in 69% yield.

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 210 nm), t_{minor} = 10.9 min, t_{major} = 12.2 min; ee = 95%.

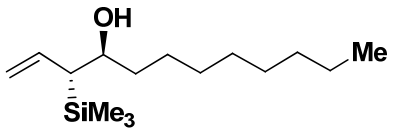


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.888	BB	0.2039	4741.20605	364.03851	49.9308
2	12.265	VB	0.2382	4754.34570	311.30685	50.0692



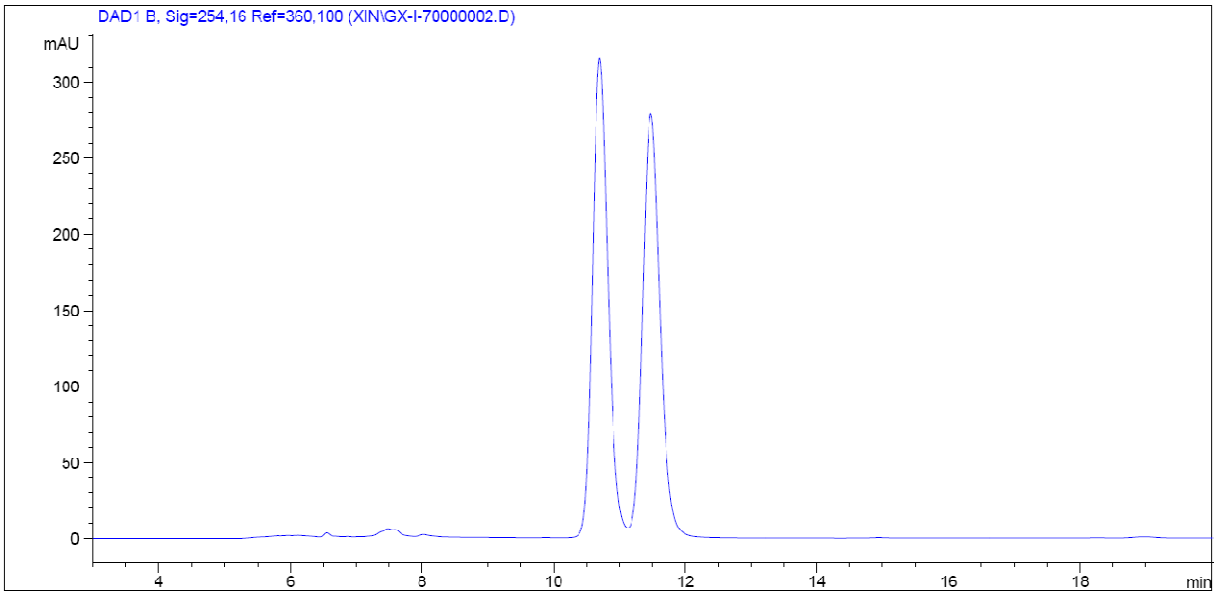
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.858	VB	0.1991	743.34534	58.17200	2.4271
2	12.180	BB	0.3342	2.98835e4	1463.67444	97.5729

(3*R*,4*S*)-3-(trimethylsilyl)dodec-1-en-4-ol (2.3c)

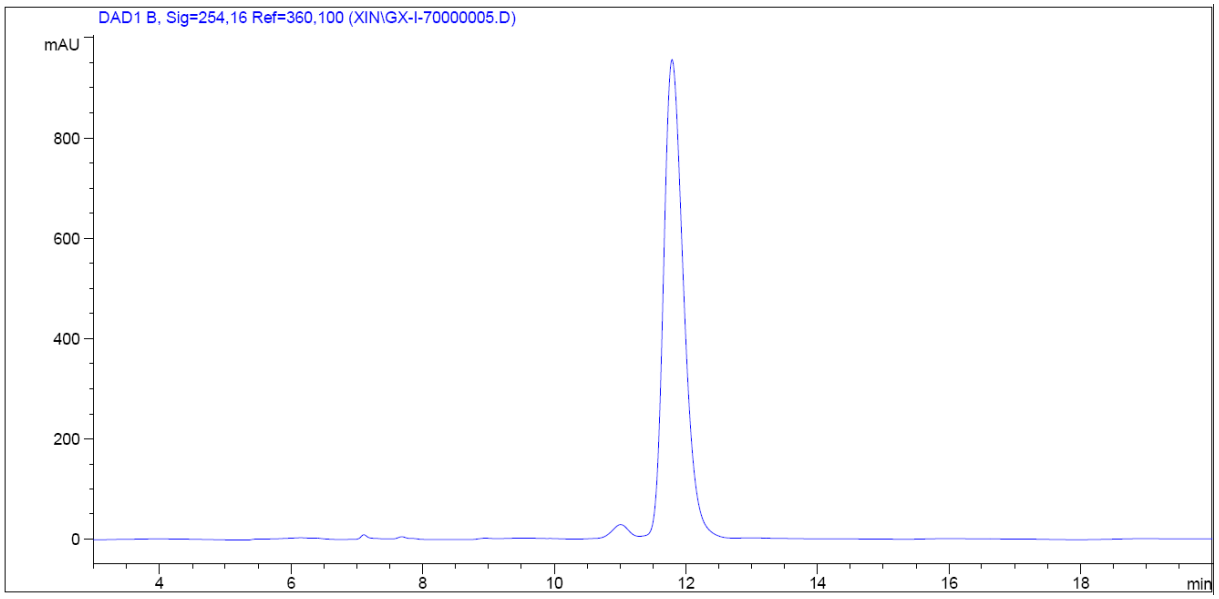


An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with nonan-1-ol **2.2c** (28.9 mg, 0.20 mmol, 100 mol%), *(R)*-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%) and α-(trimethylsilyl)allyl acetate (103 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **2.3c** (34.4 mg, 0.134 mmol) as a colorless oil in 67% yield.

HPLC: Enantiomeric excess was determined by HPLC analysis of the 3,5-nitrobenzoate derivative of the product (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 254 nm), t_{minor} = 11.0 min, t_{major} = 11.8 min; ee = 95%.

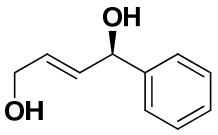


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.696	BV	0.2546	5203.19336	315.17252	50.3147
2	11.472	VB	0.2851	5138.10547	278.73831	49.6853



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.007	BV	0.2837	527.41931	28.26665	2.5487
2	11.788	VB	0.3263	2.01666e4	955.05286	97.4513

(*R*,*E*)-1-phenylbut-2-ene-1,4-diol (2.5f)



A flask was charged with **2.3f** (33.1 mg, 0.15 mmol, 100 mol%), K_2CO_3 (103.7 mg, 0.75 mmol, 500 mol%) and acetone (1.25 mL). The mixture was cooled to -20 ^oC, and then 0.08 M solution of dimethyl dioxirane in acetone (3.75 mL, 0.3 mmol, 200 mol%) was added. The resulting mixture was warmed to 0 ^oC and stirred until no starting material left (checked by TLC). The mixture was filtered through a pad of celite, concentrated, and treated with a solution of HOAc (0.5 mL) in MeOH (3 mL) for 30 min. The solution was diluted with ether and washed with sat'd aqueous $NaHCO_3$ solution. The aqueous layer was extracted with ether. The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ether) provided **2.5f** (19.5 mg, 0.119 mmol) as a colorless oil in 79% yield. (*E*:*Z* = 5:1)

TLC (SiO_2): R_f = 0.4 (ethyl acetate:ether, 1:40).

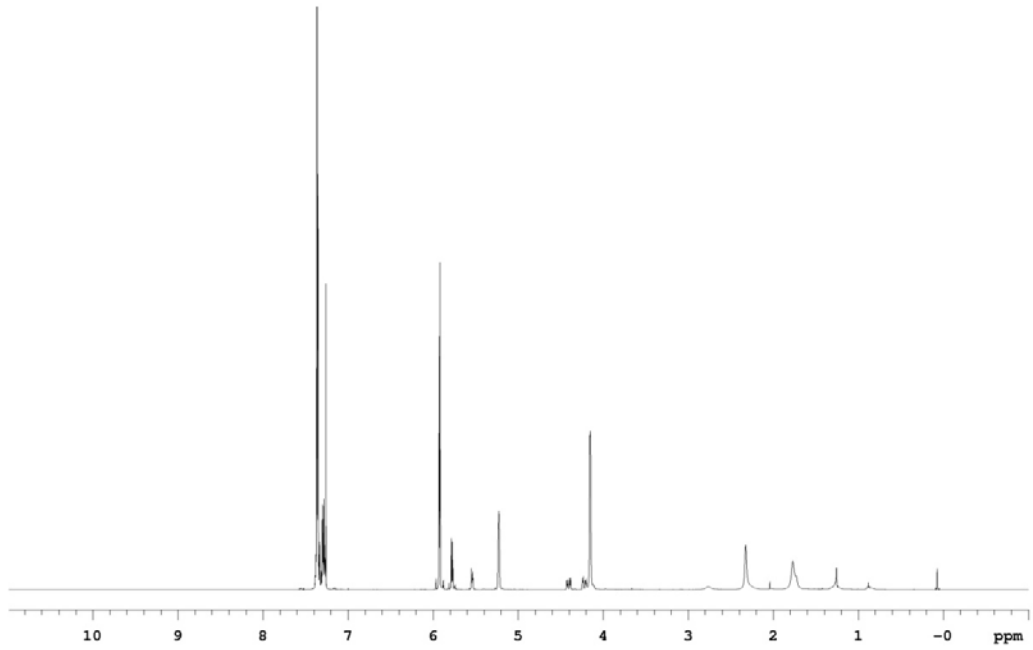
^{1}H NMR for the major product (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 5.93-5.92 (m, 2H), 5.25-5.20 (m, 1H), 4.15 (d, *J* = 2.0 Hz, 2H), 2.32 (br, 1H), 1.77 (br, 1H).

^{13}C NMR for the major product (100 MHz, $CDCl_3$): δ 142.7, 133.4, 130.2, 128.6, 127.8, 126.2, 74.8, 63.1.

FTIR (neat): υ 3304, 3029, 2859, 1492, 1452, 1261, 1193, 1086, 970, 912, 846, 751.

HRMS (CI) Calcd. for $C_{10}H_{11}O_2$ $[M-H]^+$: 163.0759, Found: 163.0760.

The spectroscopic properties of this compound were consistent with the data available in the literature.[8]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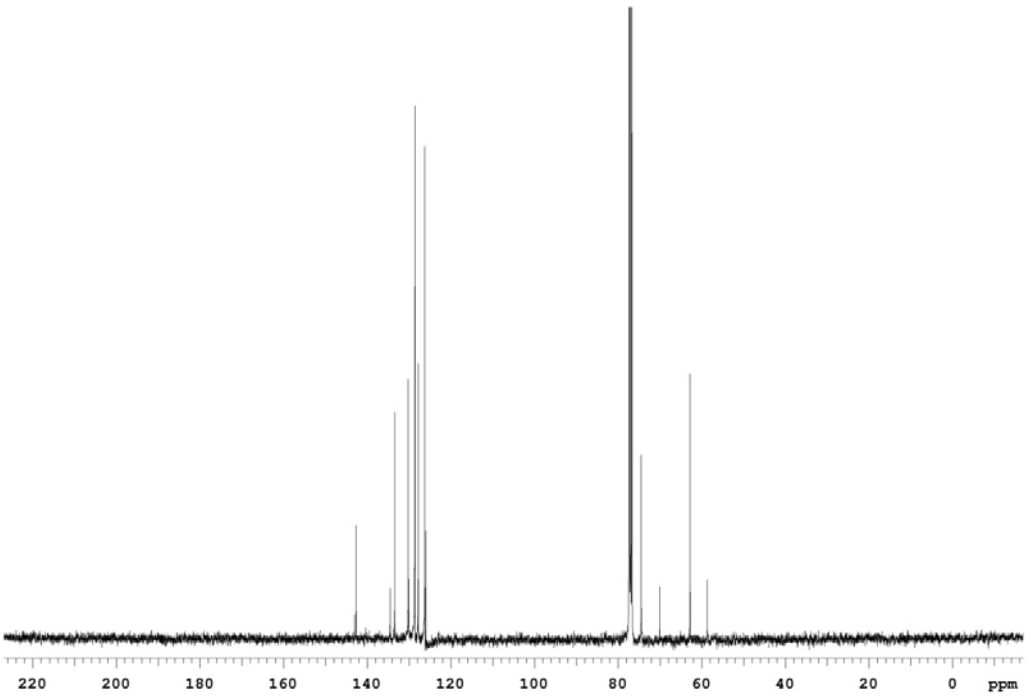
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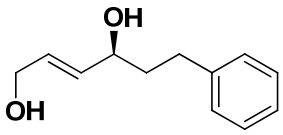
(*S*,*E*)-6-phenylhex-2-ene-1,4-diol (2.5a)



A flask was charged with **2.3a** (37.3 mg, 0.15 mmol, 100 mol%), K_2CO_3 (103.7 mg, 0.75 mmol, 500 mol%) and acetone (1.25 mL). The mixture was cooled to -20 ^oC, and then 0.08 M solution of dimethyl dioxirane in acetone (3.75 mL, 0.3 mmol, 200 mol%) was added. The resulting mixture was warmed to 0 ^oC and stirred until no starting material left (checked by TLC). The mixture was filtered through a pad of celite, concentrated, and treated with a solution of HOAc (0.5 mL) in MeOH (3 mL) for 30 min. The solution was diluted with ether and washed with sat'd aqueous $NaHCO_3$ solution. The aqueous layer was extracted with ether. The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ether) provided **2.5a** (24.2 mg, 0.126 mmol) as a colorless oil in 84% yield. (*E*:*Z* = 10:1)

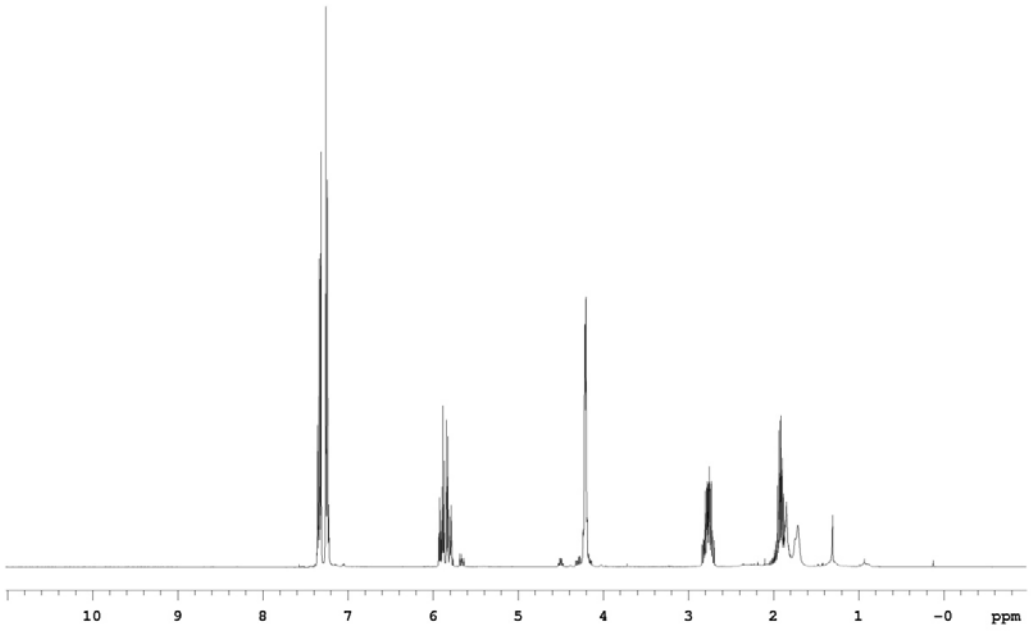
TLC (SiO_2): R_f = 0.4 (ethyl acetate:ether, 1:40).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.31 (m, 2H), 7.26-7.22 (m, 2H), 5.93-5.87 (m, 1H), 5.84-5.78 (m, 1H), 4.24-4.19 (m, 3H), 2.84-2.70 (m, 2H), 1.99-1.86 (m, 2H), 1.85 (br, 1H), 1.71 (br, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7, 134.1, 130.0, 128.4, 128.4, 125.9, 71.6, 62.9, 38.6, 31.6.

FTIR (neat): υ 3323, 3026, 2924, 2859, 1496, 1454, 1093, 998, 972, 912, 746, 699.

HRMS (CI) Calcd. for $C_{12}H_{16}O_2$ $[M]^+$: 192.1150, Found: 192.1151.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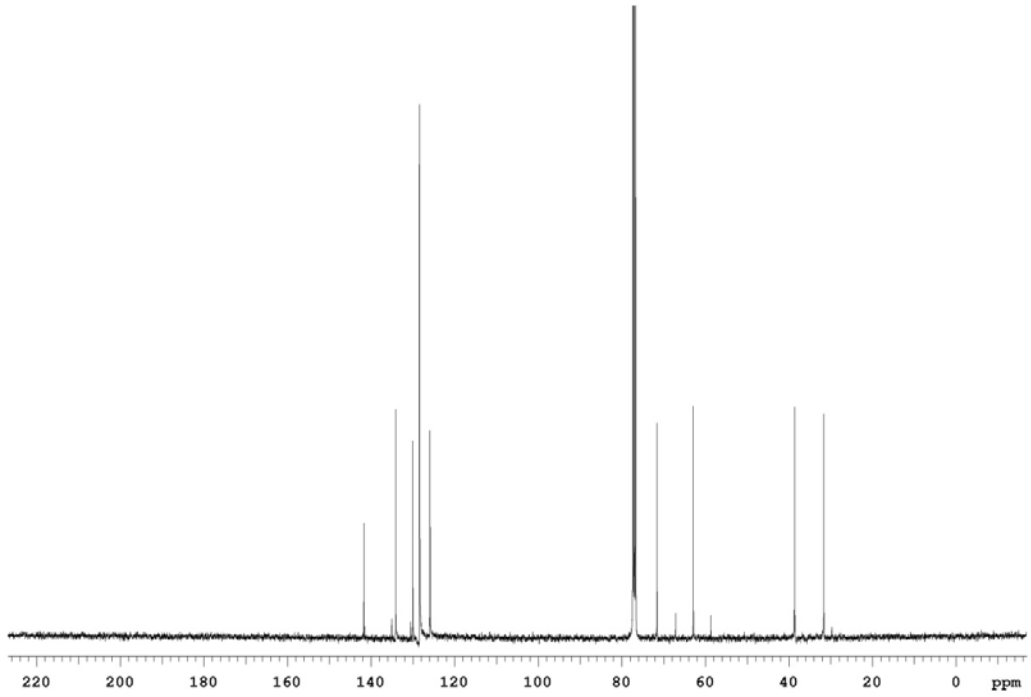
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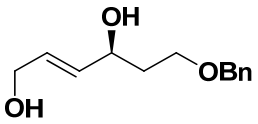
(*S*,*E*)-6-(benzyloxy)hex-2-ene-1,4-diol (2.5g)



A flask was charged with **2.3g** (41.8 mg, 0.15 mmol, 100 mol%), K_2CO_3 (103.7 mg, 0.75 mmol, 500 mol%) and acetone (1.25 mL). The mixture was cooled to -20 ^oC, and then 0.08 M solution of dimethyl dioxirane in acetone (3.75 mL, 0.3 mmol, 200 mol%) was added. The resulting mixture was warmed to 0 ^oC and stirred until no starting material left (checked by TLC). The mixture was filtered through a pad of celite, concentrated, and treated with a solution of HOAc (0.5 mL) in MeOH (3 mL) for 30 min. The solution was diluted with ether and washed with sat'd aqueous $NaHCO_3$ solution. The aqueous layer was extracted with ether. The combined organic layers was dried over Na_2SO4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ether) provided **2.5g** (29.3 mg, 0.132 mmol) as a colorless oil in 88% yield. (*E*:*Z* = ≥20:1)

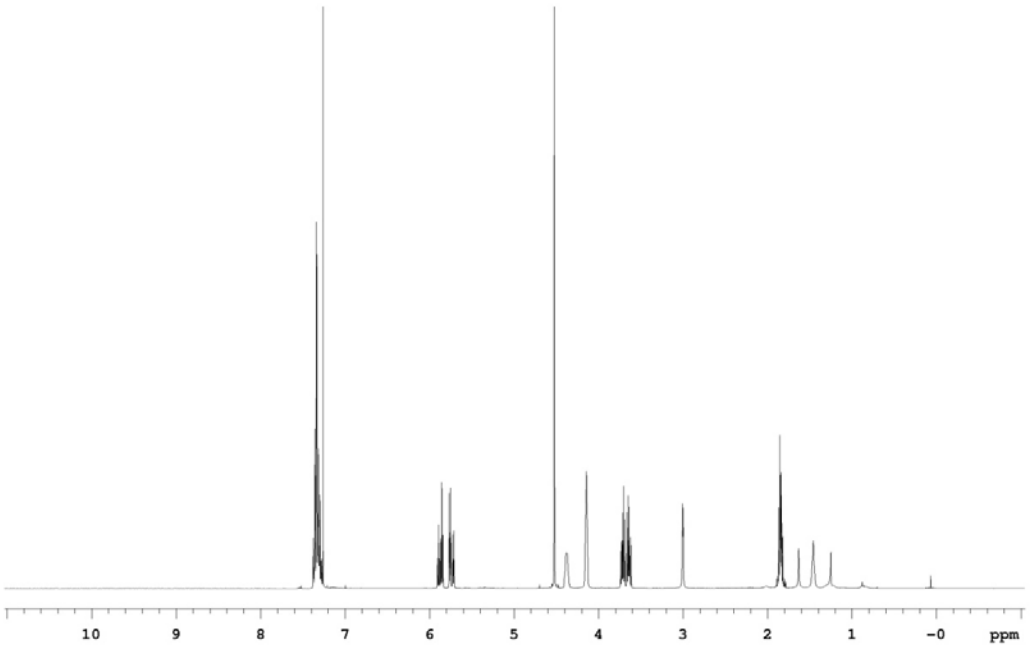
TLC (SiO_2): R_f = 0.4 (ethyl acetate:ether, 1:40).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83-7.30 (m, 5H), 5.87 (dtd, *J* = 15.6, 5.2, 1.2 Hz, 1H), 5.74 (ddt, *J* = 15.6, 6.0, 1.2 Hz, 1H), 4.52 (s, 2H), 4.41-4.34 (m, 1H), 4.17-4.12 (m, 2H), 3.74-3.61 (m, 2H), 3.00 (d, *J* = 3.6 Hz, 1H), 1.88-1.79 (m, 2H), 1.46 (br, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 133.6, 129.5, 128.5, 127.8, 127.7, 73.3, 71.2, 68.4, 63.0, 36.4.

FTIR (neat): υ 3346, 2921, 2860, 1496, 1454, 1414, 1364, 1310, 1206, 1072, 1004, 969, 909, 802, 736.

HRMS (CI) Calcd. for $C_{13}H_{17}O_3$ $[M-H]^+$: 221.1178, Found: 222.1181.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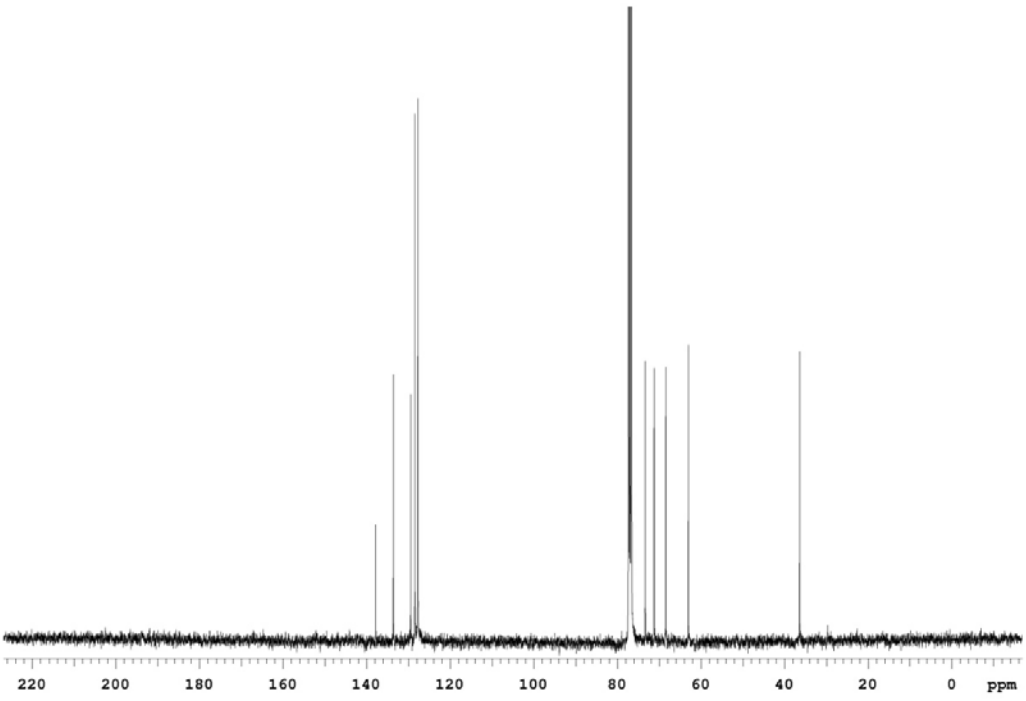
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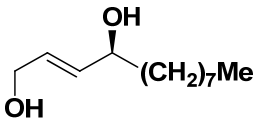
(*S*,*E*)-dodec-2-ene-1,4-diol (2.5c)



A flask was charged with **2.3c** (38.5 mg, 0.15 mmol, 100 mol%), K_2CO_3 (103.7 mg, 0.75 mmol, 500 mol%) and acetone (1.25 mL). The mixture was cooled to -20 ^oC, and then 0.08 M solution of dimethyl dioxirane in acetone (3.75 mL, 0.3 mmol, 200 mol%) was added. The resulting mixture was warmed to 0 ^oC and stirred until no starting material left (checked by TLC). The mixture was filtered through a pad of celite, concentrated, and treated with a solution of HOAc (0.5 mL) in MeOH (3 mL) for 30 min. The solution was diluted with ether and washed with sat'd aqueous $NaHCO_3$ solution. The aqueous layer was extracted with ether. The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ether) provided **2.5c** (26.1 mg, 0.131 mmol) as a colorless oil in 87% yield. (*E*:*Z* = 10:1)

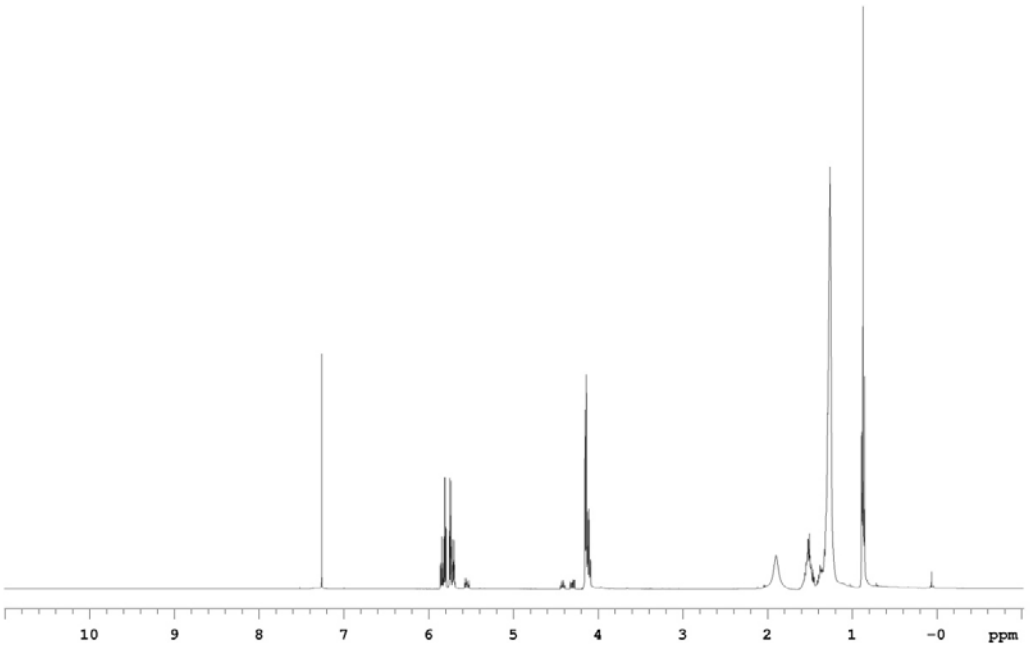
TLC (SiO_2): R_f = 0.5 (ethyl acetate:ether, 1:40).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89-5.79 (m, 1H), 5.76-5.69 (m, 1H), 4.15-4.09 (m, 3H), 1.90 (br, 2H), 1.57-1.45 (m, 2H), 1.33-1.20 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 134.5, 129.7, 72.3, 62.9, 37.2, 31.8, 29.5, 29.2, 25.4, 25.3, 22.6, 14.1.

FTIR (neat): υ 3332, 2854, 1465, 1085, 1005, 971, 722.

HRMS (CI) Calcd. for $C_{12}H_{23}O_2$ $[M-H]^+$: 199.1698, Found: 199.1699.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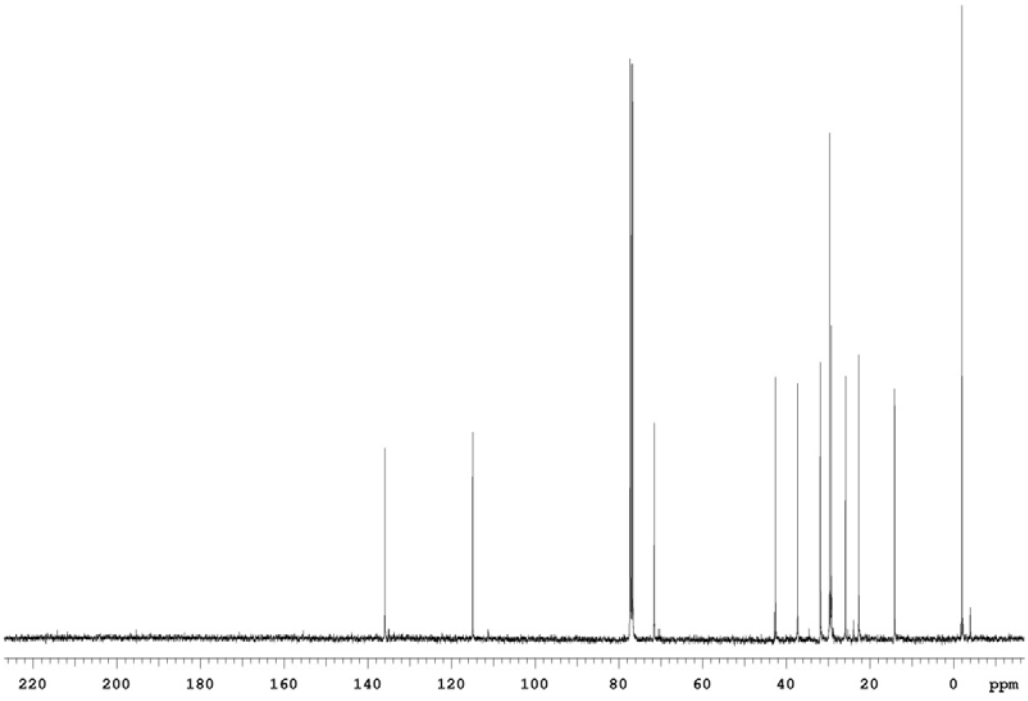
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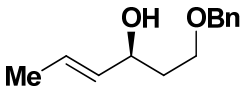
(*S*,*E*)-1-(benzyloxy)hex-4-en-3-ol (2.6g)



A flask was charged with **2.3g** (30.2 mg, 0.11 mmol, 100 mol%), 4-nitrobenzaldehyde (18.1 mg, 0.12 mmol, 110 mol%) and DCM (1.2 mL, 0.9 M). The mixture was cooled to -78 ^{o}C, and then 1.0 M solution of $TiCl_4$ in DCM (0.14 mL, 0.14 mmol, 130 mol%) was added dropwise over 3 min. The resulting mixture was stirred until no starting material left (checked by TLC). The mixture was quenched with sat'd aqueous ammonium chloride solution (3 mL) at -78 ^{o}C, and then diluted with DCM (3 mL). The resulting biphasic solution was warmed to ambient temperature and stirred for 10 min. The organic phase was separated and the aqueous was washed with DCM. The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ether:hexanes, 1:4) provided **2.6g** (16.6 mg, 0.08 mmol) as a colorless oil in 73% yield.

TLC (SiO_2): R_f = 0.15 (ethyl acetate:hexanes, 1:4).

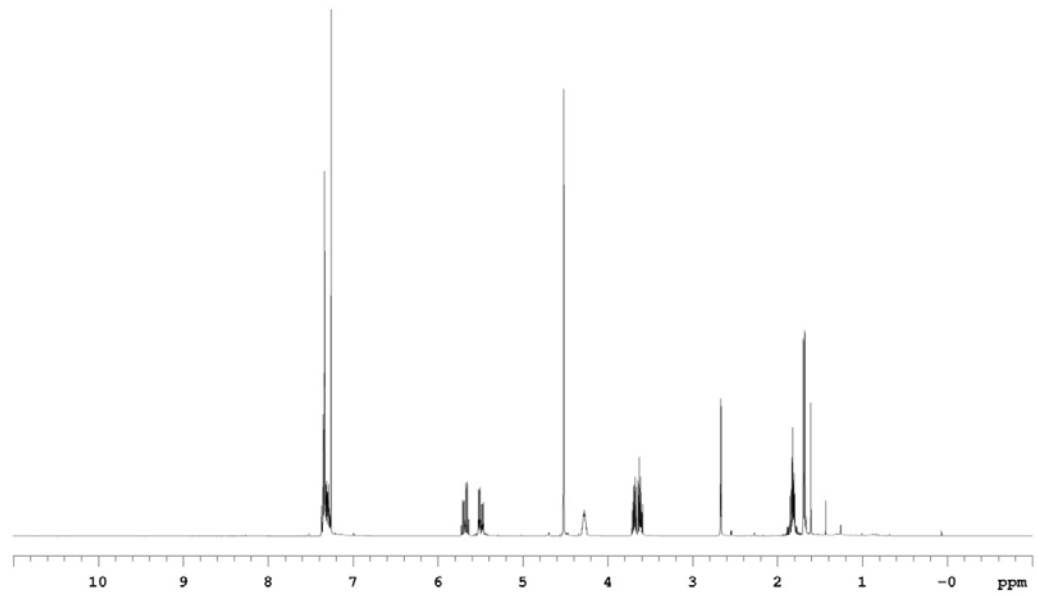
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.37 (m, 5H), 5.67 (dqd, *J* = 15.2, 6.4, 0.8 Hz, 1H), 5.49 (dqd, *J* = 15.2, 6.4, 1.6 Hz, 1H), 4.52 (s, 2H), 4.25-4.31 (m, 1H), 3.72-3.66 (m, 1H), 3.65-3.59 (m, 1H), 2.67 (d, *J* = 3.2 Hz, 1H), 1.85-1.75 (m, 2H), 1.69 (ddd, *J* = 6.8, 1.6, 0.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 133.5, 128.4, 127.7, 127.6, 126.4, 73.2, 71.8, 68.4, 36.7, 17.7.

FTIR (neat): υ 3414, 3029, 2916, 2857, 1496, 1453, 1364, 1309, 1205, 1096, 966, 923, 801, 736.

HRMS (CI) Calcd. for $C_{13}H_{17}O_2$ $[M-H]^+$: 205.1229, Found: 205.1227.

The spectroscopic properties of this compound were consistent with the data available in the literature[9].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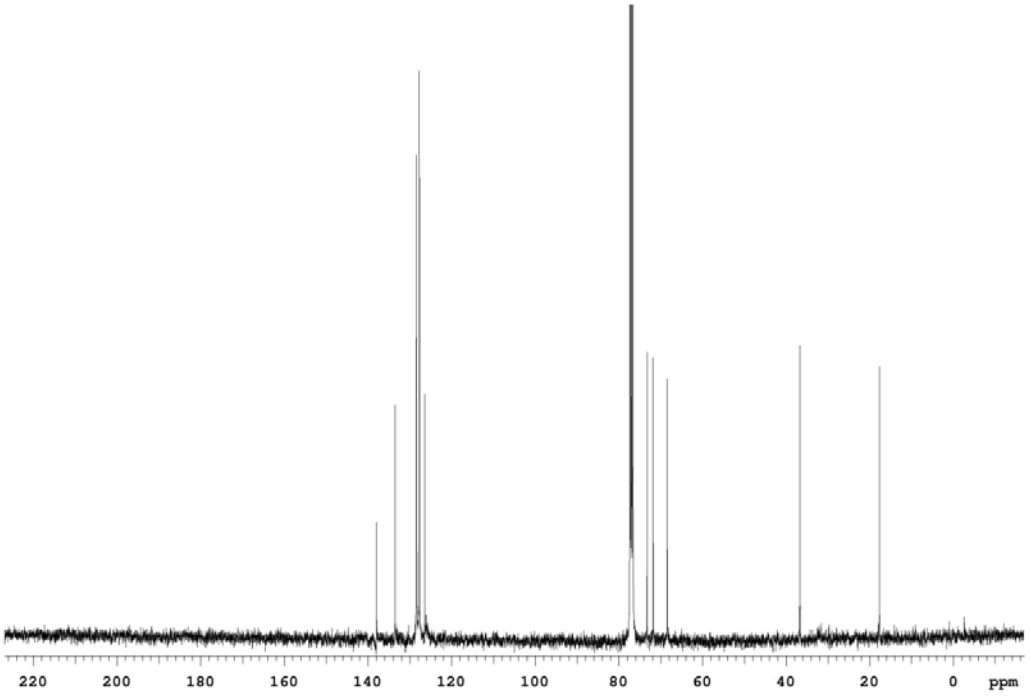
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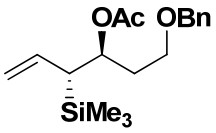
ppm

(3*S*,4*R*)-1-(benzyloxy)-4-(trimethylsilyl)hex-5-en-3-yl acetate (2.3g-OAc)



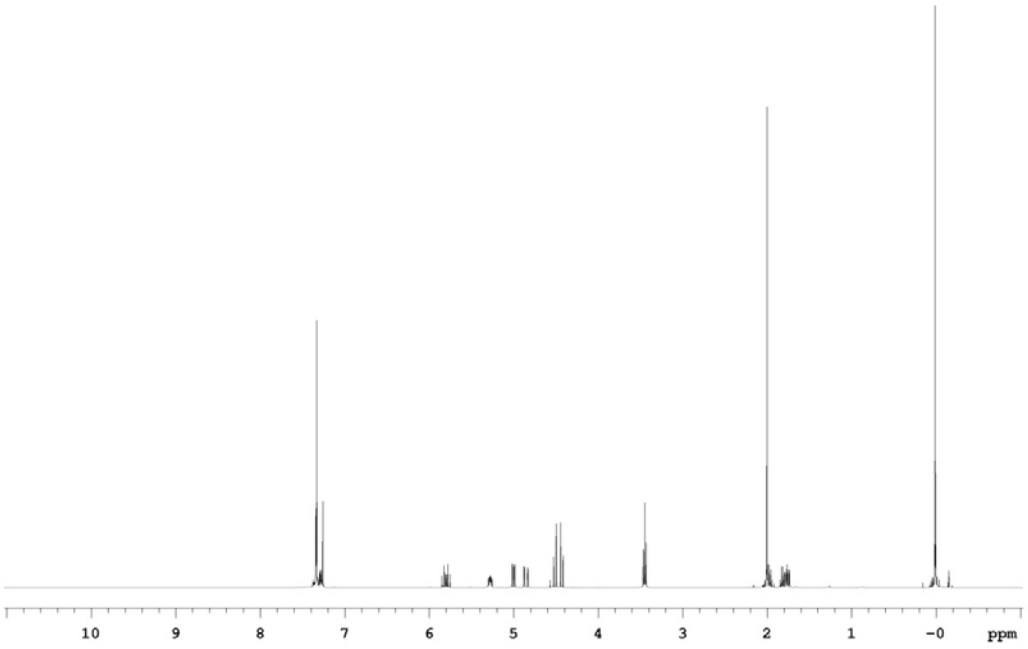
To a cooled (0 °C) suspension of **2.3g** (100 mg, 0.36 mmol, 100 mol%), DMAP (4.4 mg, 0.036 mmol, 10 mol%) and Et_3N (72.9 mg, 0.72 mmol, 200 mol%) in DCM (4.0 mL, 0.09 M) was added acetic anhydride (73.8 mg, 0.72 mmol, 200 mol%). The reaction mixture was allowed to warm to ambient temperature and stirred overnight. The mixture was washed with sat'd aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:30 with 0.1% TEA) provided **2.3g-OAc** (114.2 mg, 0.36 mmol) as a colorless oil in 99% yield.

TLC (SiO_2): R_f = 0.70 (ethyl acetate:hexanes, 1:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.25 (m, 5H), 5.80 (dt, *J* = 17.2, 10.4 Hz, 1H), 5.28 (dq, *J* = 6.0, 3.6 Hz, 1H), 5.00 (dd, *J* = 10.4, 2.0 Hz, 1H), 4.85 (ddd, *J* = 17.2, 2.0, 0.4 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.43 (d, *J* = 12.0 Hz, 1H), 3.45 (t, *J* = 6.4 Hz, 2H), 2.05-1.92 (m, 1H), 2.00 (s, 3H), 1.84-1.74 (m, 2H), 0.01 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 138.4, 135.0, 128.3, 127.8, 127.5, 115.2, 72.9, 71.9, 66.7, 40.0, 34.3, 21.3, -2.4.

FTIR (neat): υ 3031, 2954, 2860, 1737, 1626, 1496, 1454, 1370, 1236, 1102, 1019, 953, 902, 838, 748, 697.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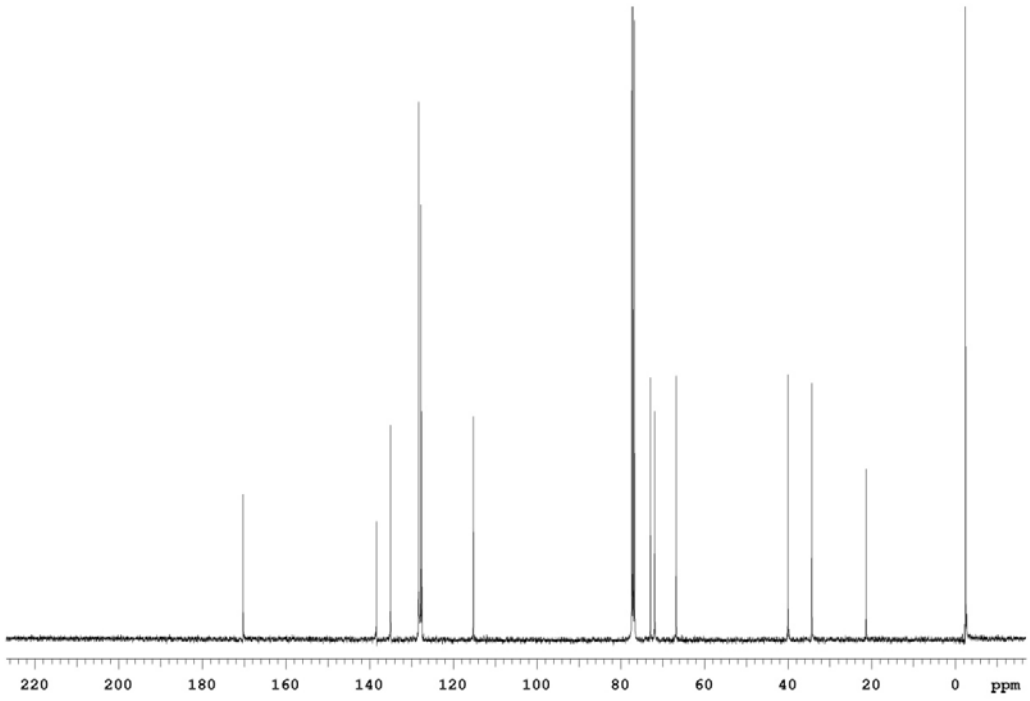
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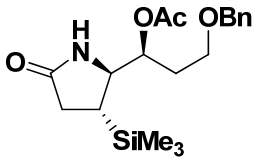
ppm

(1*S*)-3-(benzyloxy)-1-((3*R*)-5-oxo-3-(trimethylsilyl)pyrrolidin-2-yl)propyl acetate (2.7g)



To a cooled (0 ^{o}C) suspension of **2.3g-OAc** (15 mg, 0.047 mmol, 100 mol%) and $NaHCO_3$ (10 mg, 0.12 mmol, 250 mol%) in toluene (0.5 mL, 0.1 M) was added chlorosulfonyl isocynate (10.9 mg, 0.071 mmol, 150 mol%). The reaction mixture was warmed slowly to ambient temperature and stirred for 10 hr. Sat'd aqueous $NaHSO_3$ (0.5 mL) was added and stirred 16 hr, at which point the layers were separated and the aqueous was extracted with EtOAc. The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:2.5) provided **2.7g** (13.3 mg, 0.037 mmol) as a colorless oil in 78% yield.

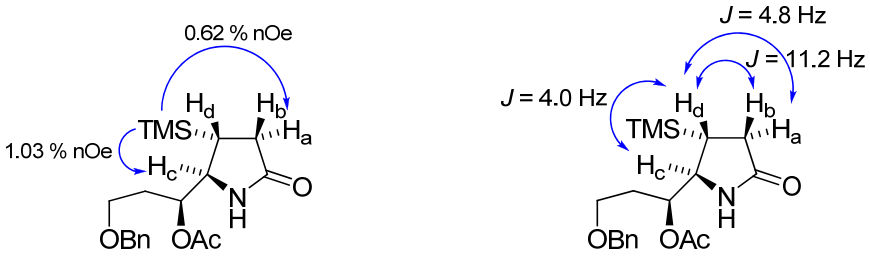
TLC (SiO_2): R_f = 0.2 (ethyl acetate:hexanes, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.27 (m, 5H), 6.41 (br, 1H), 4.95-4.91 (m, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 3.63 (t, *J* = 4.0 Hz, 1H), 3.56-3.42 (m, 2H), 2.55 (dd, *J* = 17.6, 11.2 Hz, 1H), 2.10 (dd, *J* = 17.6, 4.8, 1H), 2.04 (s, 3H), 1.94-1.81 (m, 2H), 1.32 (ddd, *J* = 11.2, 4.8, 4.0 Hz, 1H), 0.01 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.2, 170.6, 137.8, 128.4, 127.9, 127.8, 73.8, 73.4, 66.1, 57.7, 31.4, 31.3, 22.0, 21.1, -3.8.

FTIR (neat): υ 3211, 2953, 1737, 1691, 1496, 1454, 1370, 1232, 1096, 1027, 964, 837, 738, 698.

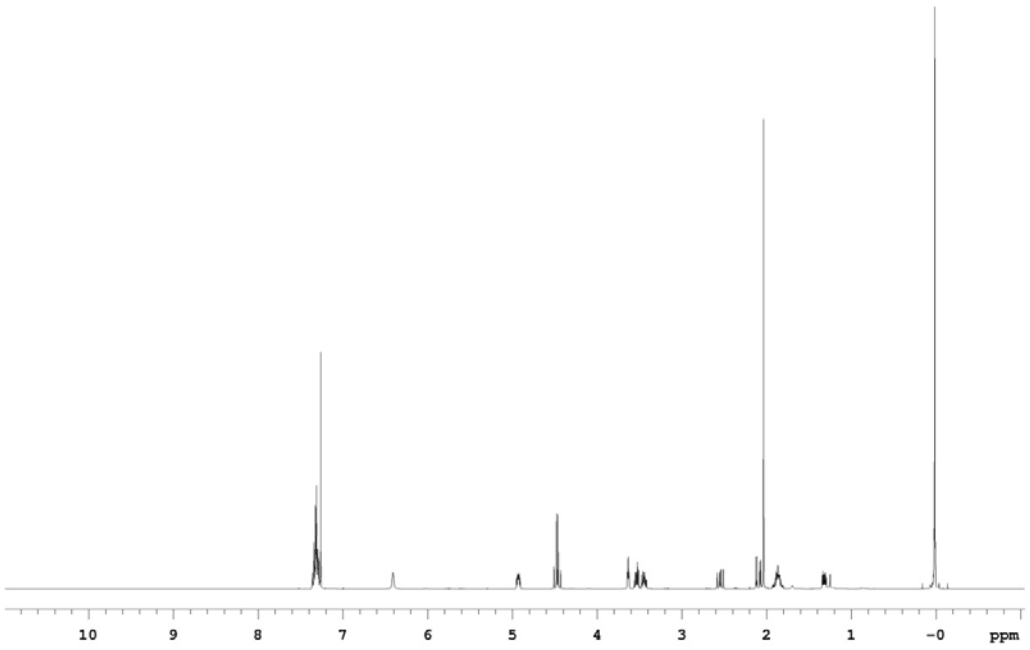
HRMS (CI) Calcd. for $C_{19}H_{30}NO_4Si$ $[M+H]^+$: 364.1944, Found: 364.1946.



NOE experiment was performed for **7g** using a pure sample.

TMS irradiated: H_a (0.62%), H_C (1.03%).

(Note: The observation of nOe between TMS and H_c and the absence of nOe between TMS and the OAc suggest a 1,2 trans configuration which is corresponding to the coupling constant calculation and the stereochemistry model proposed by Woerpel.)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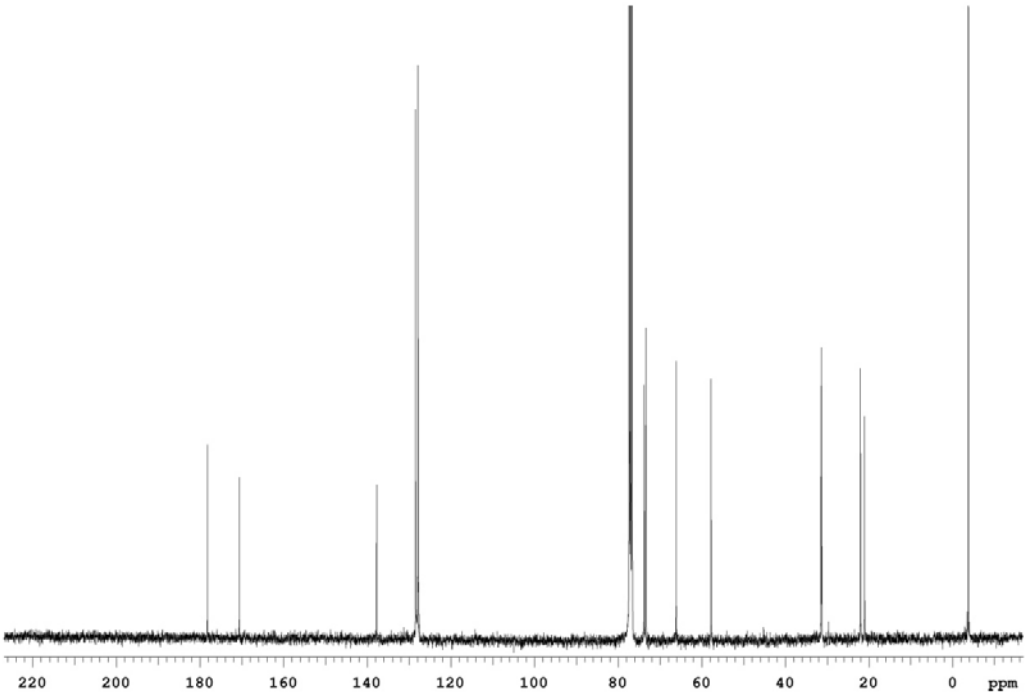
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CHAPTER 3: IRIDIUM CATALYZED ANTI-DIASTEREO- AND ENANTIOSELECTIVE CARBONYL (A-TRIFLUOROMETHYL)ALLYLATION[1]

3.1 INTRODUCTION

It is estimated that 20% of approved pharmaceutical agents and 30-40% of commercially available agrochemicals contain one or more fluorine atoms.[2] Additionally, in 2006, 80% of the small molecule drugs entering the market were estimated to contain one or more chiral centers.[3] These facts underscore the importance of developing enantioselective methods for the preparation of organofluorine compounds.[3,4] Toward this end, highly enantioselective nucleophilic trifluoromethylations of aldehydes and ketones have been developed.[4,5] Nucleophilic (α-trifluoromethyl)allylation might also serve to establish absolute stereochemistry at CF_3-bearing carbon centers.[6] Yet despite persistent efforts aimed at the development of asymmetric carbonyl allylation protocols,[7] enantioselective carbonyl (α-trifluoromethyl)allylation remains an unmet challenge.[5,6] Here, under the conditions of C-C bond forming transfer hydrogenation,[8] we report the first examples of enantioselective carbonyl (α-trifluoromethyl)allylation: a process in which carbonyl addition occurs with equal facility from the alcohol or aldehyde oxidation level. (Figure 3.1)

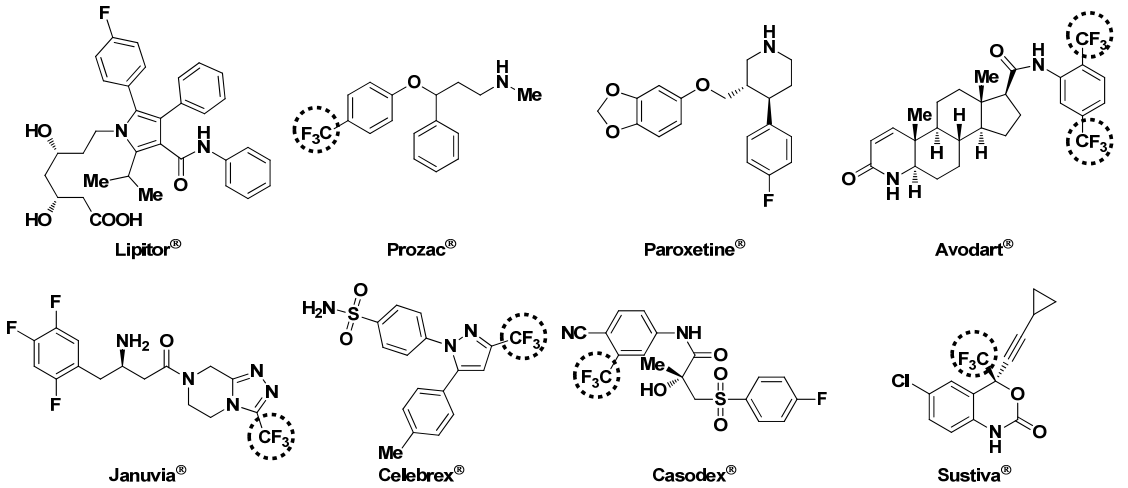
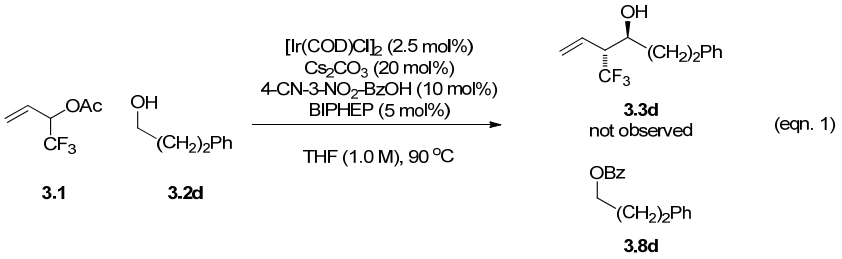


Figure 3.1 Selected Example of Pharmeceuticals bearing F and/or CF_3.

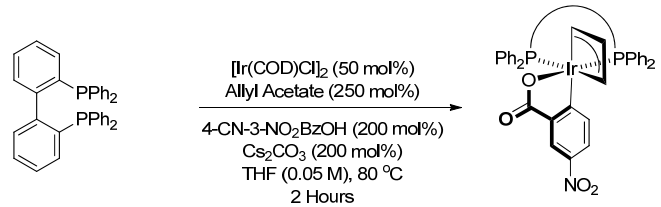
3.2 REACTION OPTIMIZATION

Our approach takes advantage of carbonyl allylation protocols recently developed in our laboratory, wherein primary alcohol dehydrogenation triggers reductive generation of allyliridium nucleophiles, enabling carbonyl allylation from the alcohol oxidation level.[8,9] In initial experiments, carbonyl (α-trifluoromethyl)allylation was attempted using the *ortho*-cyclometallated catalyst generated *in situ* from $[Ir(cod)Cl]_2$, various 4-substituted-3-nitrobenzoic acids, BIPHEP (2,2'-bis(diphenylphosphino)biphenyl) and α-trifluoromethyl allyl benzoate **3.1** in THF (1 M). However, C-C coupling products were not observed in reactions involving *in situ* catalyst generation. Rather, products of transesterification, the benzoates **3.8d** derived from alcohols **3.2d**, were obtained (eqn. 1). Eventually, it was found that transesterification is suppressed for reactions employing the isolated π-allyl iridium *C,O*-benzoate modified by BIPHEP and 4-cyano-3-nitrobenzoic acid in THF (0.2 M) (eqn. 2). As observed in related (α-trimethylsilyl)allylations,[9k] the

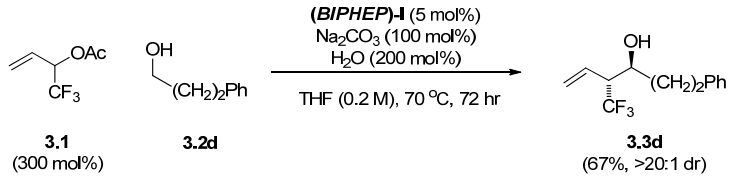
presence of water (200 mol%) improved conversion and suppressed byproduct formation, including formation of transesterification products (eqn. 3).



(eqn. 1)



(eqn. 2)



(eqn. 3)

At this point, an assay of chiral ligands was undertaken and it was found that the iridium complex modified by (*R*)-Cl,MeO-BIPHEP, designated "(*R*)-**I**", provided the highest levels of enantiomeric enrichment.(Table 3.1)

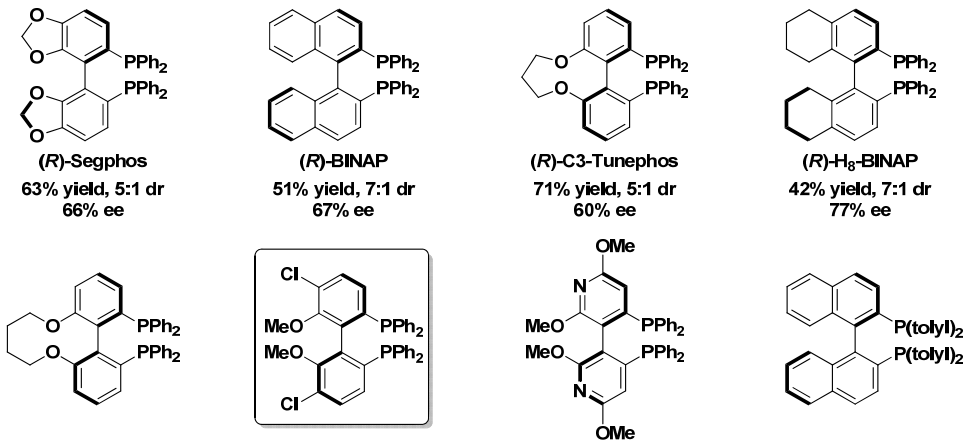
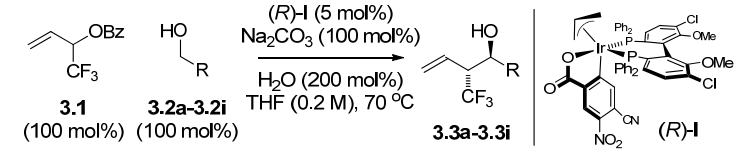
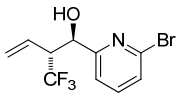


Table 3.1 Ligand optimization for enantioselective reactions.

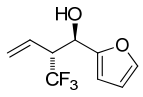
Thus, upon exposure of primary alcohols 1a-1i to α-trifluoromethyl allyl benzoate in the presence of (*R*)-**I**, Na_2CO_3 (100 mol%) and water (200 mol%) in THF (0.2 M) at 70 ^{o}C, the desired products of (α-trifluoromethyl)allylation **3.3a**-**3.3i** were generated in moderate to good yields with high levels *anti*-diastereo- and enantioselectivity (Table 3.2).



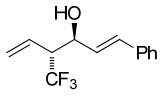
1a, R = 6-Br-2-Pyr
1b, R = 2-Furyl
1c, R = CH=CHPh
1d, R = $(CH_2)_2$Ph
1e, R = $(CH_2)_7$Me
1f, R = *c*-C_6H_{11}
1g, R = CH_2OBn
1h, R = $(CH_2)_2$OBn
1i, R = $(CH_2)_2$NHBoc



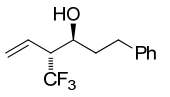
60% Yield, ≥ 20:1 dr
95% ee, **3a**



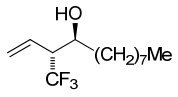
70% Yield, ≥ 20:1 dr
94% ee, **3b**



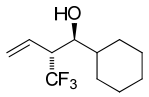
60% Yield, ≥ 20:1 dr
87% ee, **3c**



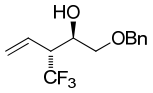
61% Yield, ≥ 20:1 dr
94% ee, **3d**



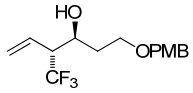
64% Yield, ≥ 10:1 dr
92% ee, **3e**



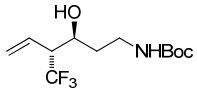
77% Yield, ≥ 20:1 dr
91% ee, **3f**



57% Yield, ≥ 20:1 dr
99% ee, **3g**



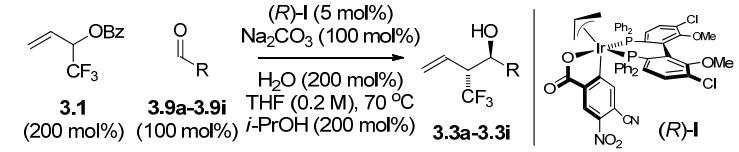
63% Yield 10:1 dr
94% ee, **3h**



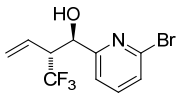
73% Yield, ≥ 20:1 dr
96% ee, **3i**

Table 3.2 *anti*-Diastereo- and enantioselective carbonyl (α-trifluoromethyl)allylation from the alcohol oxidation level.

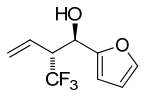
Notably, in the presence of isopropanol, but under otherwise equivalent conditions, an identical set of adducts **3.3a-3.3i** are generated from aldehydes **3.9a-3.9i** with similar levels of relative and absolute stereocontrol (Table 3.3).



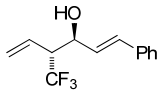
9a, R = 6-Br-2-Pyr
9b, R = 2-Furyl
9c, R = CH=CHPh
9d, R = $(CH_2)_2$Ph
9e, R = $(CH_2)_7$Me
9f, R = *c*-C_6H_{11}
9g, R = CH_2OBn
9h, R = $(CH_2)_2$OBn
9i, R = $(CH_2)_2$NHBoc



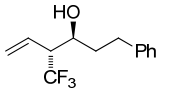
72% Yield, ≥ 20:1 dr
95% ee, **3a**



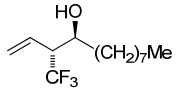
69% Yield, ≥ 20:1 dr
95% ee, **3b**



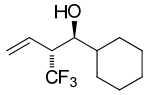
67% Yield, ≥ 20:1 dr
89% ee, **3c**



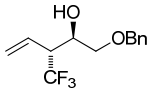
65% Yield, ≥ 20:1 dr
94% ee, **3d**



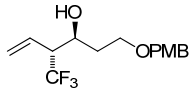
69% Yield, 10:1 dr
92% ee, **3e**



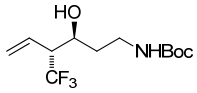
81% Yield, ≥ 20:1 dr
93% ee, **3f**



55% Yield, ≥ 20:1 dr
99% ee, **3g**



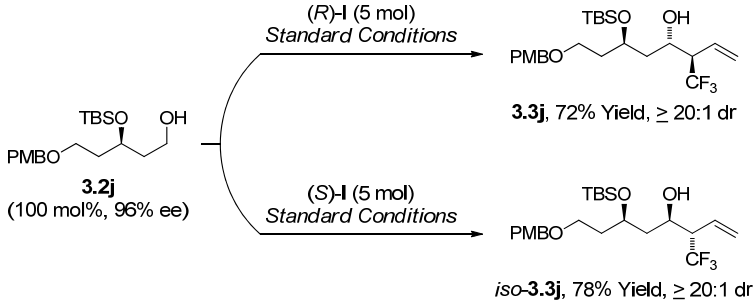
67% Yield 10:1 dr
93% ee, **3h**



70% Yield, ≥ 20:1 dr
97% ee, **3i**

Table 3.3 *anti*-Diastereo- and enantioselective carbonyl (α-trifluoromethyl)allylation from the aldehyde oxidation level.

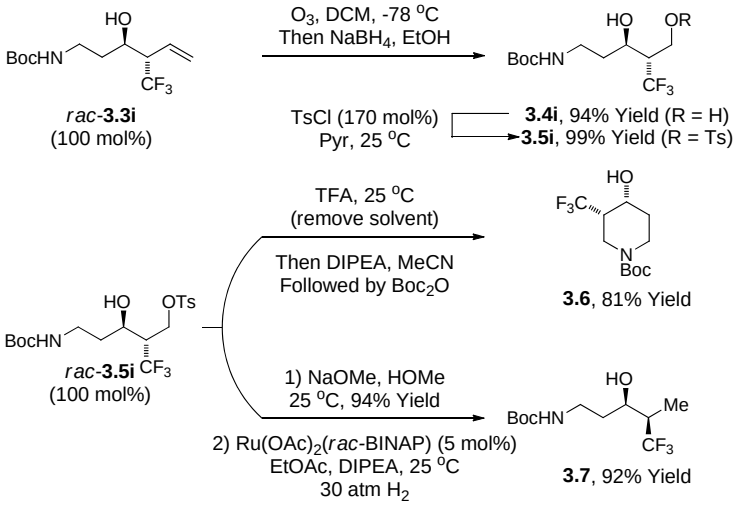
Exposure of optically enriched alcohol **3.2j** to standard conditions for *anti*-diastereo- and enantioselective (α-trifluoromethyl)allylation employing (*R*)-**I** as the precatalyst produces compound **3.3j** as a single stereoisomer, as determined by ^{1}H and ^{19}F NMR analysis. Similarly, using (*S*)-**I** as the precatalyst, alcohol **3.2j** is converted to the isomeric adduct *iso*-**3.3j** as a single stereoisomer, as determined by ^{1}H and ^{19}F NMR analysis. Using the catalyst modified by the achiral ligand, BIPHEP, compounds **3.3j** and *iso*-**3.3j** are produced in a 1:1.5 ratio, respectively. These data illustrate how the present methodology enables incorporation of CF_3-groups into polyketide substructures with high levels of catalyst directed stereoselectivity (Scheme 3.1).[10]



Scheme 3.1 Catalyst directed diastereoselectivity.

3.3 APPLICATION OF ADDUCTS

To further illustrate the utility of the coupling products, compound **3.3i** was subjected to ozonolysis conditions involving $NaBH_4$-mediated decomposition of the ozonide. The resulting β-trifluoromethyl alcohol **3.4i** was produced in 94% isolated yield. The primary alcohol of diol **3.4i** was converted chemoselectively to the primary *p*-toluenesulfonate **3.5i** in 99% isolated yield. Conversion of *p*-toluenesulfonate **3.5i** to piperidine **3.6i** was accomplished in analogy to an established procedure.[11] Alternatively, elimination of *p*-toluenesulfonate **3.5i** followed by hydrogenation of the resulting terminal olefin provides the *syn*-1,1,1-trifluoroisopropyl secondary alcohol **3.7** as a single diastereomer, as determined by ^1H and ^{19}F NMR (Scheme 3.2).[12]



Scheme 3.2 Elaboration of carbonyl (α-trifluoromethyl)allylation products.

3.4 SUMMARY

In summary, we report the first protocol for *anti*-diastereo- and enantioselective carbonyl (α-trifluoromethyl)allylation. Notably, through the use of C-C bond forming transfer hydrogenation, carbonyl addition is possible from the alcohol oxidation level, bypassing discrete alcohol oxidation and use of stoichiometric organometallic reagents and, hence, molar metallic byproducts.

3 .5 EXPERIMENTAL SECTION

General Methods

All reactions were run under an atmosphere of Argon. Tetrahydrofuran (THF) and toluene were obtained from Pure-Solv MD-5 Solvent Purification System (Innovative Technology). Anhydrous solvents were transferred by an oven-dried syringe. Sealed tubes (13x100 mm) were purchased from Fischer Scientific and were dried in an oven overnight and cooled under a stream of nitrogen prior to use. Commercially available allyl acetate (Aldrich) was purified by distillation prior to use. Cesium carbonate was purchased from Alfa Aesar and was used directly without further purification. Isopropanol (Fisher) was purified by distillation prior to use. Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F_{254}). Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M or M-H) or a suitable fragment ion. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) spectra were recorded with a Varian Gemini (400 MHz) spectrometer for $CDCl_3$ solutions and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δ_H (7.26 ppm) and $CDCl_3$ δ_C (77.0 ppm), respectively, as internal standards. Coupling constants are reported in Hertz (Hz).

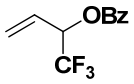
Preparation of (*R*)-I

To a mixture of $[Ir(cod)Cl]_2$ (87.3 mg, 0.13 mmol, 100 mol%), (*R*)-Cl,MeO-BIPHEP (169 mg, 0.26 mmol, 200 mol%), Cs_2CO_3 (169 mg, 0.52 mmol, 400 mol%), 4-CN-3-NO_2BzOH (100 mg, 0.52 mmol, 400 mol%) and allyl acetate (65 mg, 0.65 mmol, 500 mol%) in a sealed tube under an atmosphere of N_2 was added THF (2.6 mL, 0.05 M). The reaction mixture was stirred for 30 minutes at ambient temperature and heated for 1.5 hours at 80 ^oC, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was filtered with the aid of THF (10 mL). The filtrate was concentrated *in vacuo* and desolved in THF (2 mL). Hexanes (50 mL) was added. A yellow precipitate formed, which was collected by filtration and dried under vacuum to provide (*R*)-**I** (238 mg, 0.221 mmol) in 85% yield.

Preparation of (*S*)-I

To a mixture of $[Ir(cod)Cl]_2$ (87.3 mg, 0.13 mmol, 100 mol%), (*S*)-Cl,MeO-BIPHEP (169 mg, 0.26 mmol, 200 mol%), Cs_2CO_3 (169 mg, 0.52 mmol, 400 mol%), 4-CN-3-NO_2BzOH (100 mg, 0.52 mmol, 400 mol%) and allyl acetate (65 mg, 0.65 mmol, 500 mol%) in a sealed tube under an atmosphere of N_2 was added THF (2.6 mL, 0.05 M). The reaction mixture was stirred for 30 minutes at ambient temperature and heated for 1.5 hours at 80 ^oC, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was filtered with the aid of THF (10 mL). The filtrate was concentrated *in vacuo* and desolved in THF (2 mL). Hexanes (50 mL) was added. A yellow precipitate formed, which was collected by filtration and dried under vacuum to provide (*S*)-**I** (238 mg, 0.221 mmol) in 85% yield.

1-(trifluoromethyl)allyl benzoate 3.1



In accordane with a modified literature procedure,[13] trifluoroacetaldehyde hydrate (10.6 g, 90 mmol, 100 mol%) was added dropwise to a mixture of H_2SO_4 (20 mL) and P_2O_5 (3 g) at 100 ^oC. The trifluoroacetaldehyde thus generated was transferred via cannula to a cooled flask (CO_2/acetone). Once all the gaseous aldehyde was collected, THF (45 mL) was added and the reaction vessel was placed in an ice bath. To the stirred solution of aldehyde at 0 ^oC was added a THF solution of vinylmagnesium bromide (110 mL, 1.0 M, 110 mmol, 110 mol%). After addition was complete, the reaction mixture was stirred at 0 ^oC for 3 h, at which point the reaction was NH_4Cl (aq.) (20 mL). The reaction mixture was filtered with the aid of ether. Triethylamine (18.2 g, 180 mmol, 200 mol%) was added to the etheral solution, followed by benzoyl chloride (19.0 g, 135 mmol, 150 mol%). The reaction mixture was stirred at ambient temperature overnight. A saturated $NaHCO_3$ (aq.) was added and the organic phase was separated and washed with water and brine. The resulting solution was dried (Na_2SO_4), filtered and concentrated *in vacuo.* Purification of the residue by column chromatography (SiO_2; hexane:ether, 10:1) provied title compound (11.0 g, 48 mmol) as a colorless oil in 53% yield.

TLC (SiO_2): R_f = 0.7 (ethyl acetate: hexanes, 1:4).

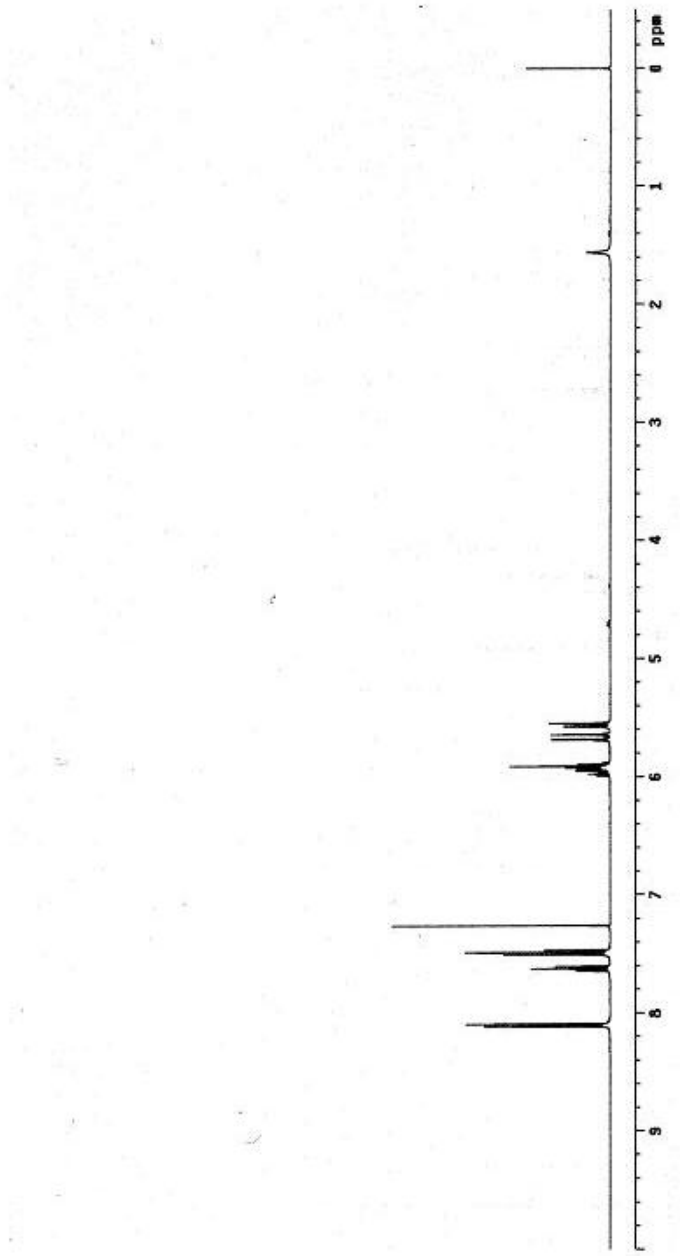
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12-8.09 (m, 2H), 7.65-7.60 (m, 1H), 7.51-7.47 (m, 2H), 5.99-5.88 (m, 2H), 5.69-5.63 (m, 1H), 5.58-5.54 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 133.8, 130.0, 128.6, 126.9, 123.3, 123.1 (q, J = 278.3 Hz), 71.3 (q, J = 33.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -76.6 (d, J = 6.4 Hz).

FTIR (neat): 3321, 2941, 1737, 1453, 1317, 1258, 1178, 1125, 1091, 1028, 985, 949, 899, 707, 685 cm^{-1}.

HRMS (CI) Calcd. for $C_{11}H_{10}O_2F_3$ $[M+H]^+$: 231.0633, Found: 231.0639.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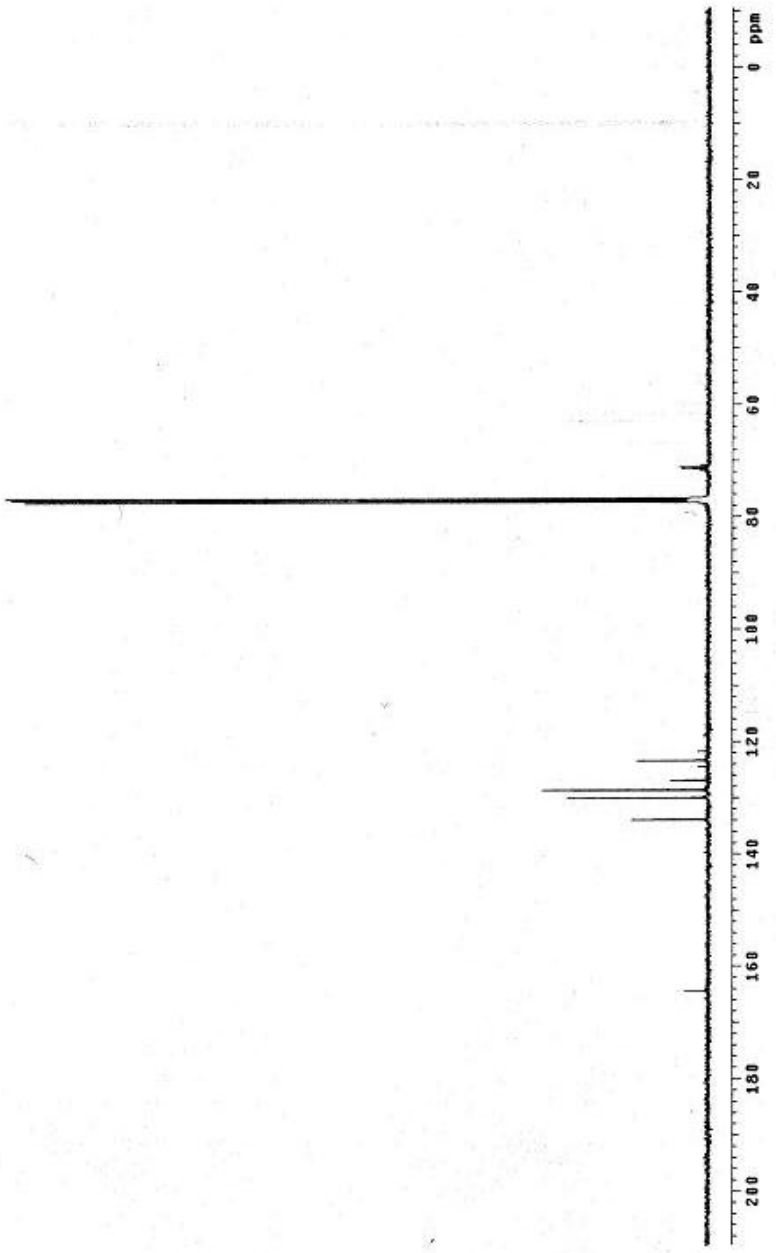
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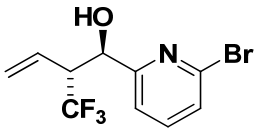
(*1R,2R*)-1-(6-bromopyridin-2-yl)-2-(trifluoromethyl)but-3-en-1-ol 3.3a



An oven-dried sealed tube under an atmosphere of N_2 was charged with (6-bromopyridin-2-yl)methanol **3.1a** (37.6 mg, 0.20 mmol, 100 mol%), (*R*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%), THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%). α-(Trifluoromethyl)allyl benzoate (92.1 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 with 0.1% TEA) provided **3.3a** (35.6 mg, 0.120 mmol) as a colorless oil in 60% yield (>20:1 dr).

TLC (SiO_2): R_f = 0.3 (ethyl acetate: hexanes, 1:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (t, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.34 (dt, *J* = 8.0, 0.8 Hz, 1H), 5.80 (dtd, *J* = 17.2, 10.4, 0.8 Hz, 1H), 5.25-5.23 (m, 2H), 5.02 (d, *J* = 17.2 Hz, 1H), 3.37-3.27 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 141.1, 139.1, 127.1, 126.1 (q, *J* = 280.5 Hz), 126.0, 123.7, 119.6, 70.4, 54.0 (q, *J* = 25.4 Hz).

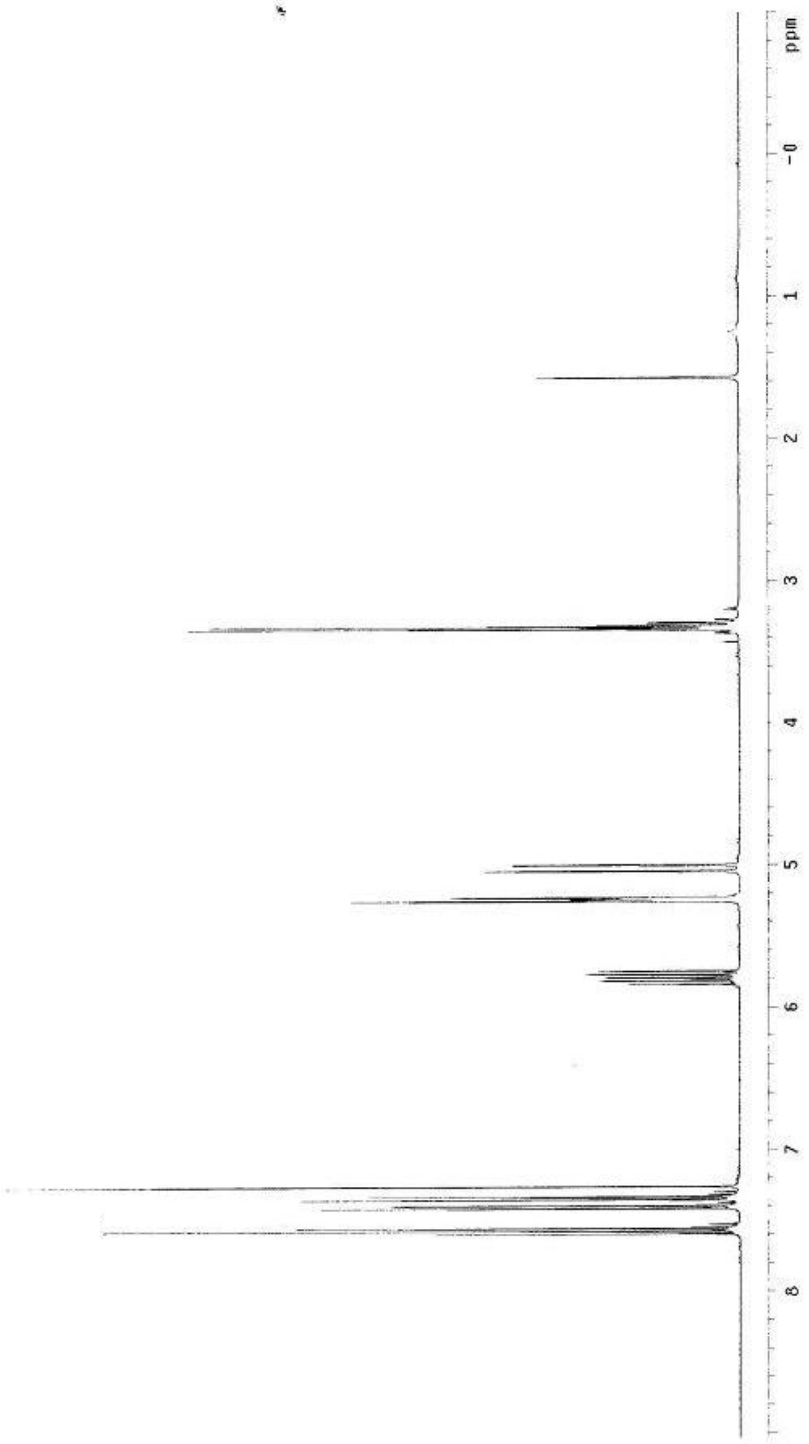
^{19}F NMR (376 MHz, $CDCl_3$): δ -67.71 (d, *J* = 9.6 Hz).

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 97:3, 1 mL/min, 254 nm), t_{major} = 9.2 min, t_{minor} = 10.9 min; ee = 95%.

[α]$_D^{25}$ = -29.55 (c =2.2, CH_2Cl_2).

FTIR (neat): 3398, 1558, 1434, 1124, 1101, 987, 936, 758, 686 cm^{-1}.

HRMS (CI) Calcd. for $C_{10}H_{10}NOF_3$ $[M+H]^+$: 295.9898, Found: 295.9898.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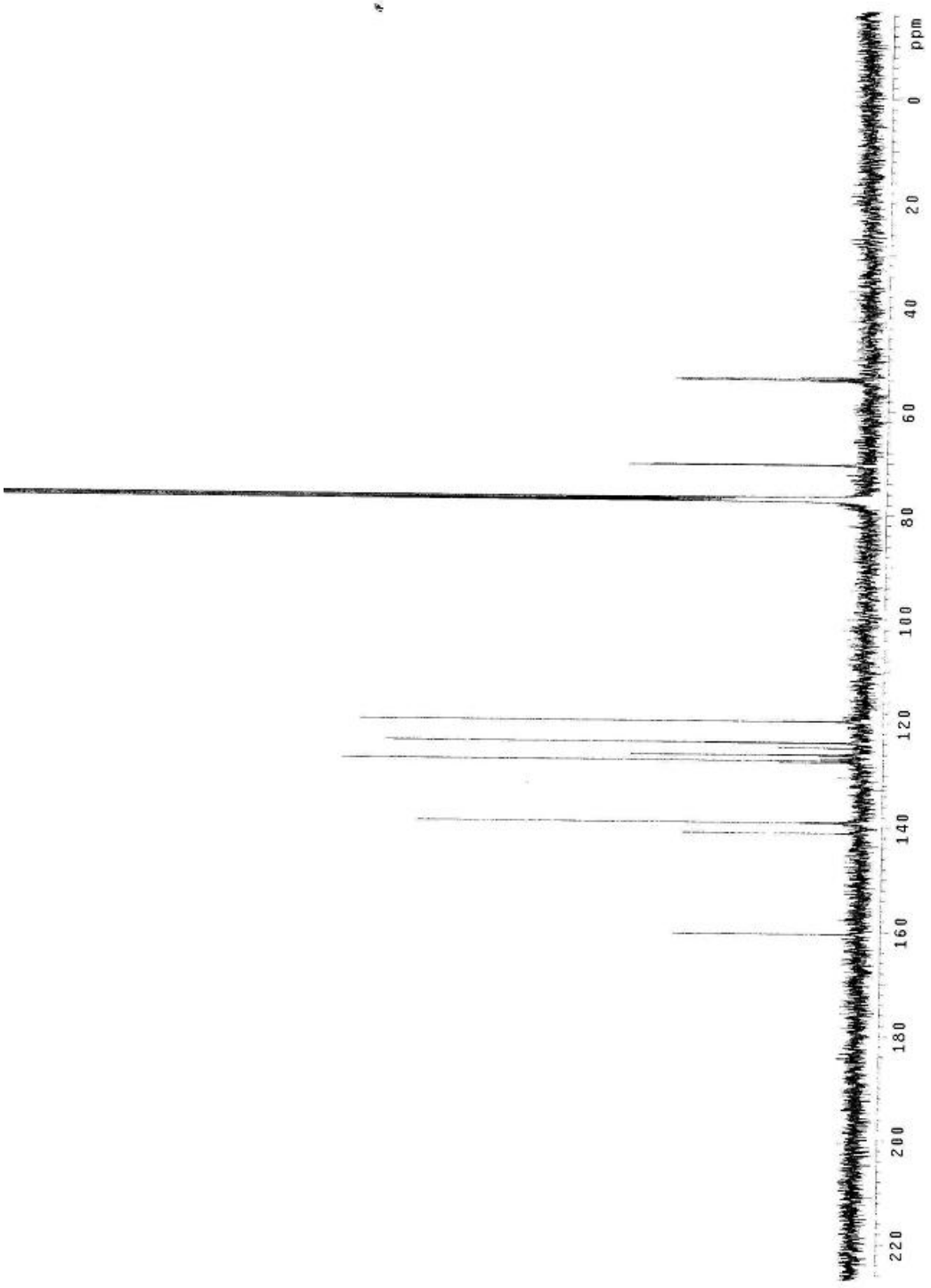
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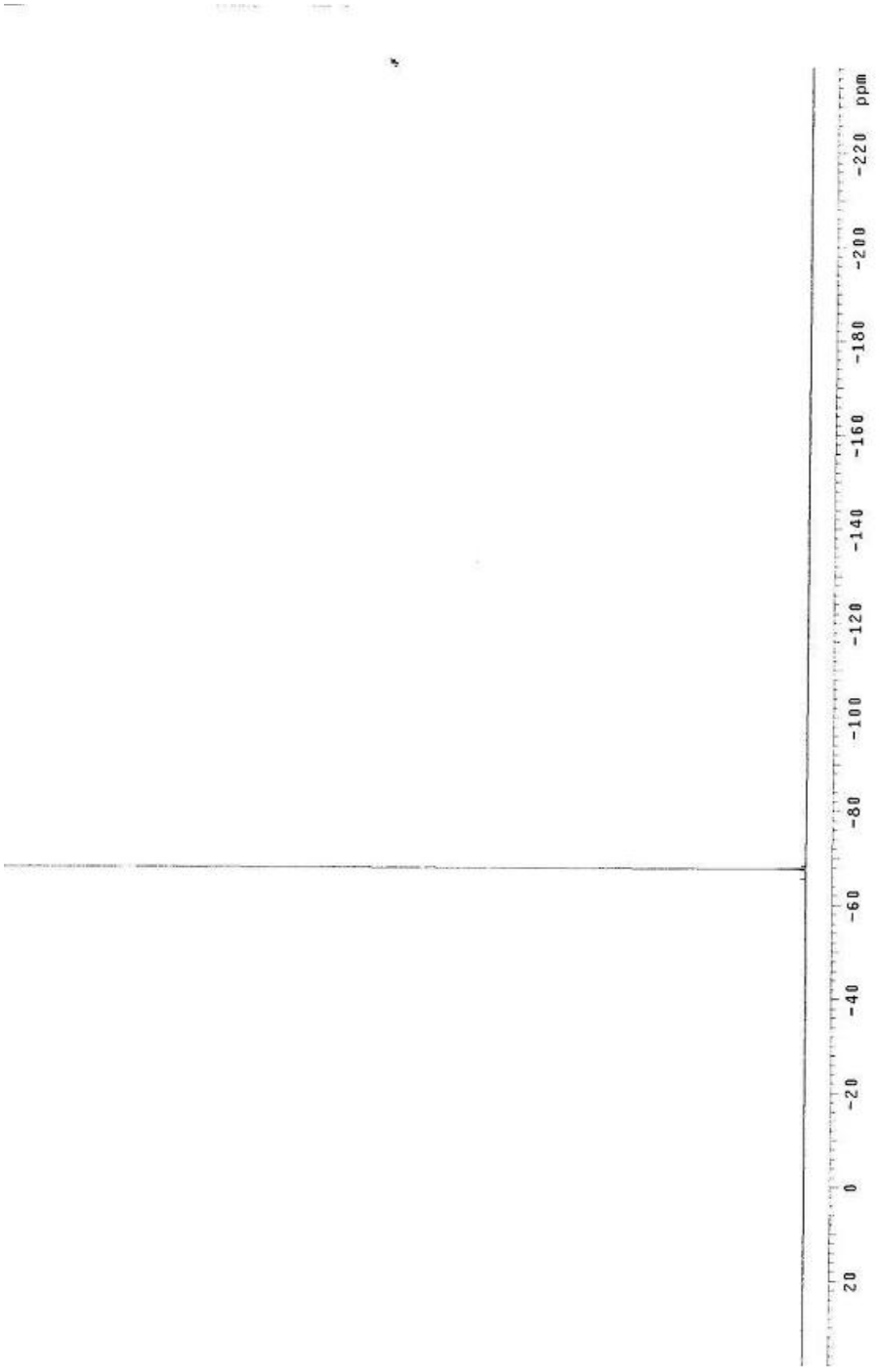
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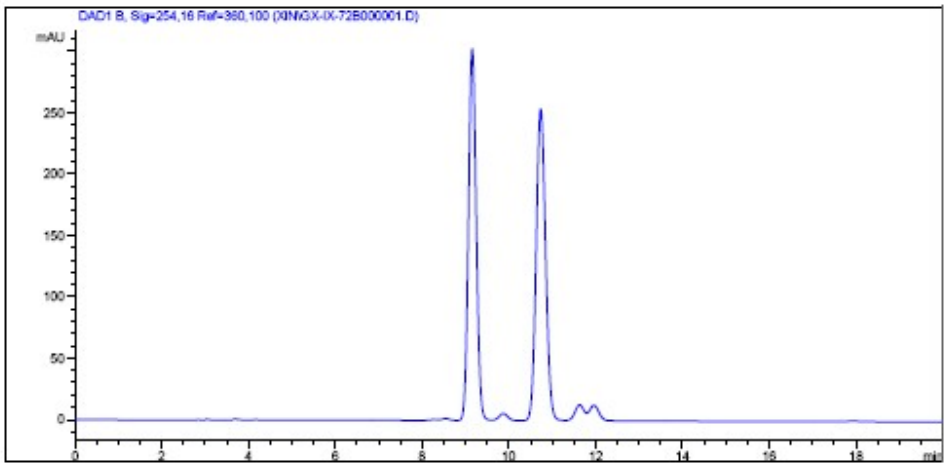

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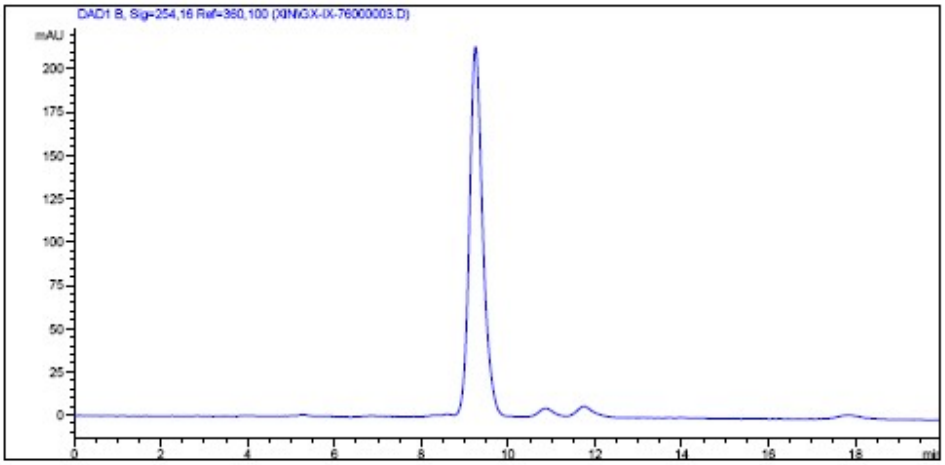

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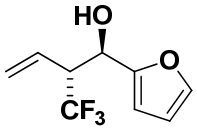
2	10.862	BV	0.2982	120.20893	4.96923	2.5779

(*1R,2R*)-1-(furan-2-yl)-2-(trifluoromethyl)but-3-en-1-ol 3.3b



An oven-dried sealed tube under an atmosphere of N_2 was charged with furan-2-ylmethanol **3.1b** (19.6 mg, 0.20 mmol, 100 mol%), (*R*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), Na_2CO_3 (21.2 mg, 0.20 mmol, 100 mol%). THF (1.0 mL, 0.2 M), H_2O (7.2 μL, 0.4 mmol, 200 mol%), and α-(trifluoromethyl)allyl benzoate (92.1 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 with 0.1% TEA) provided **3.3b** (28.9 mg, 0.140 mmol) as a colorless oil in 70% yield (>20:1 dr).

TLC (SiO_2): R_f = 0.4 (ethyl acetate: hexanes, 1:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (dt, *J* = 2.0, 0.8, 1H), 6.35 (dd, *J* = 3.6, 2.0 Hz, 1H), 6.32 (dt, *J* = 3.6, 0.8 Hz, 1H), 5.90 (dtd, *J* = 17.2, 10.4, 1.2 Hz, 1H), 5.43 (d, *J* = 10.4 Hz, 1H), 5.29 (d, *J* = 17.2 Hz, 1H), 5.17 (d, *J* = 6.0 Hz, 1H), 3.29 (pd, *J* = 9.2, 4.0 Hz, 1H), 2.17 (br, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 142.3, 126.9, 125.8 (q, *J* = 279.8 Hz,), 123.8, 110.4, 107.4, 65.8, 52.4 (q, *J* = 34.7 Hz).

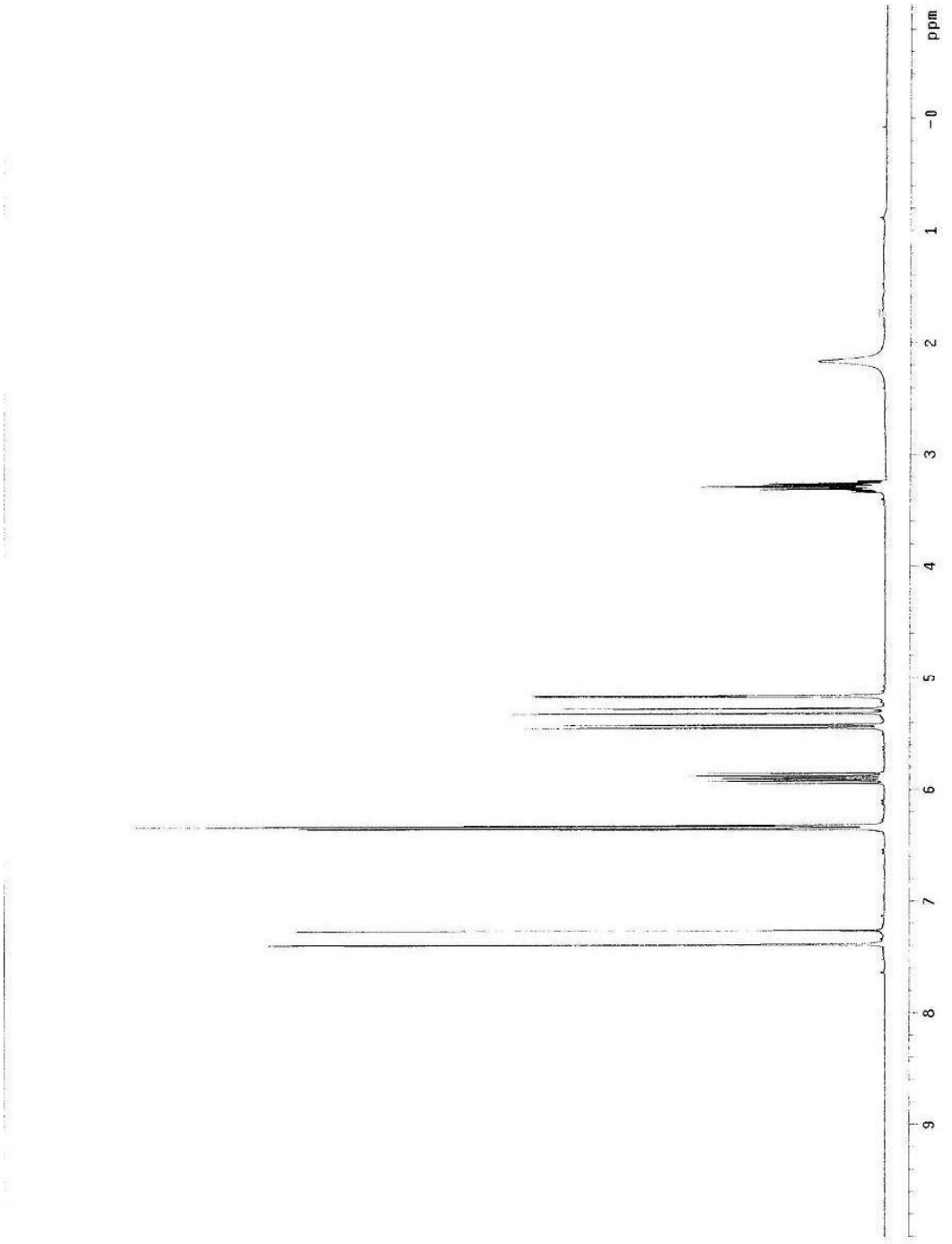
^{19}F NMR (376 MHz, $CDCl_3$): δ -68.02 (d, *J* = 10.0 Hz).

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), t_{minor} = 6.0 min, t_{major} = 6.8 min; ee = 94%.

[α]$_D^{25}$ = +15.00 (c =1.2, CH_2Cl_2).

FTIR (neat): 3408, 2918, 1506, 1352, 1172, 1257, 1152, 1132, 1010, 937, 739 cm^{-1}.

HRMS (CI) Calcd. for $C_9H_{10}F_3O_2$ $[M+H]^+$: 207.0632, Found: 207.0633.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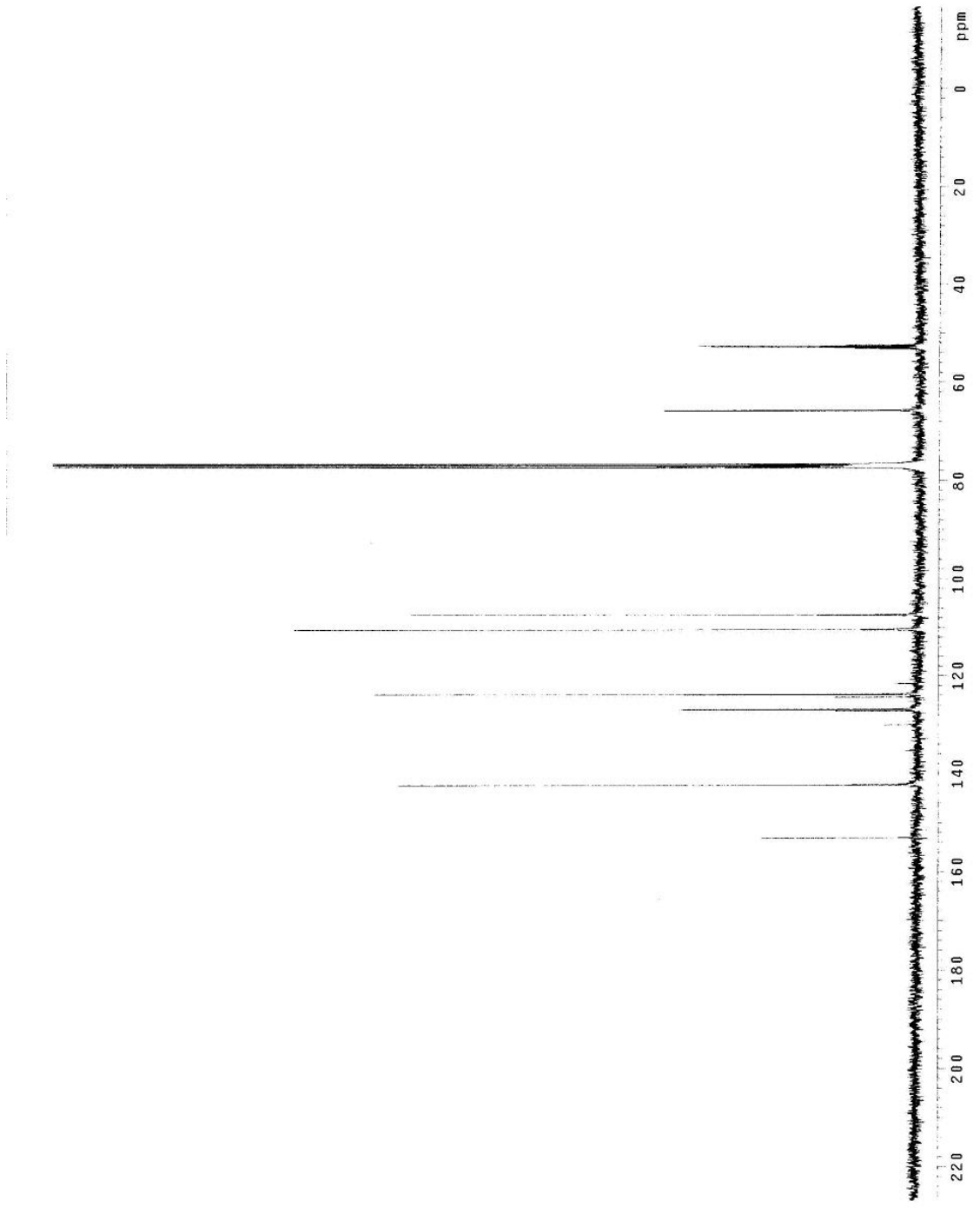
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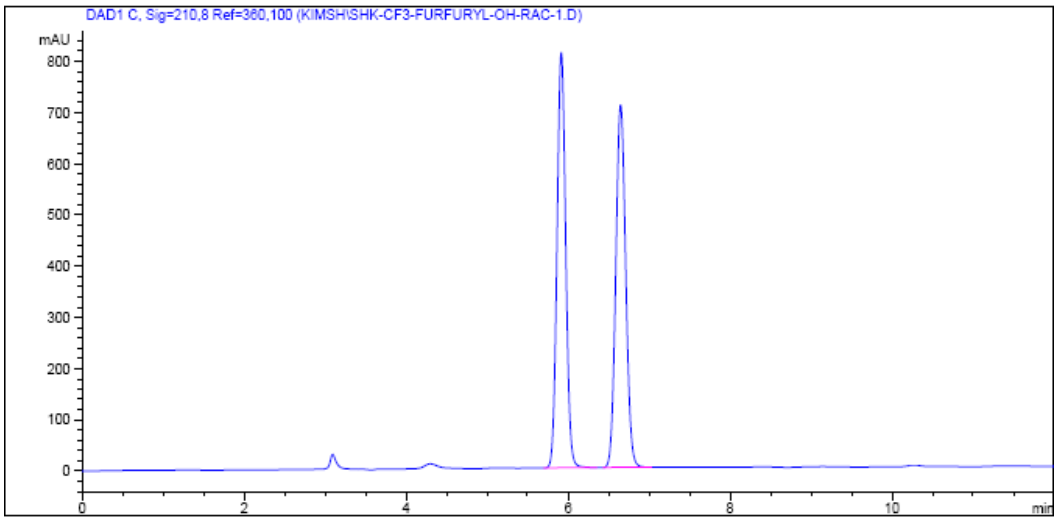

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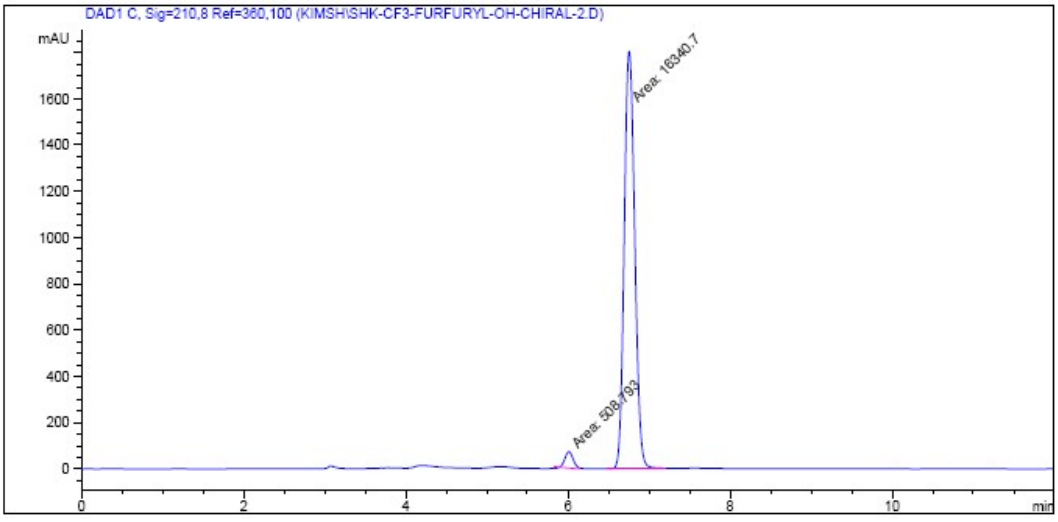

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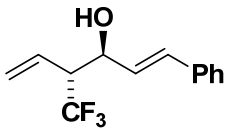
(*3S,4R,E*)-1-phenyl-4-(trifluoromethyl)hexa-1,5-dien-3-ol 3.3c



An oven-dried sealed tube under an atmosphere of N_2 was charged with *trans*-cinnamyl alcohol **3.1c** (26.8 mg, 0.20 mmol, 100 mol%), (*R*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), Na_2CO_3 (21.2 mg, 0.20 mmol, 100 mol%). THF (1.0 mL, 0.2 M), H_2O (7.2 μL, 0.4 mmol, 200 mol%), and α-(trifluoromethyl)allyl benzoate (92.1 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 with 0.1% TEA) provided **3.3c** (29.1 mg, 0.120 mmol) as a colorless oil in 60% yield (>20:1 dr).

TLC (SiO_2): R_f = 0.5 (ethyl acetate: hexanes, 1:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.25 (m, 5H), 6.67 (d, *J* = 16.0 Hz, 1H), 5.19 (ddd, *J* = 16.0, 6.8, 0.4 Hz, 1H), 5.92 (dtd, *J* = 17.2, 10.4, 0.8 Hz, 1H), 5.49 (d, *J* = 10.4 Hz, 1H), 5.47 (d, *J* = 17.2 Hz, 1H), 4.74-4.71 (m, 1H), 2.92 (pd, *J* = 8.4, 3.2 Hz, 1H), 1.9 (br, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.1, 132.4, 128.6, 128.1, 128.0 (q, *J* = 272.2 Hz), 126.6, 123.6, 70.2, 54.2 (q, *J* = 24.7 Hz).

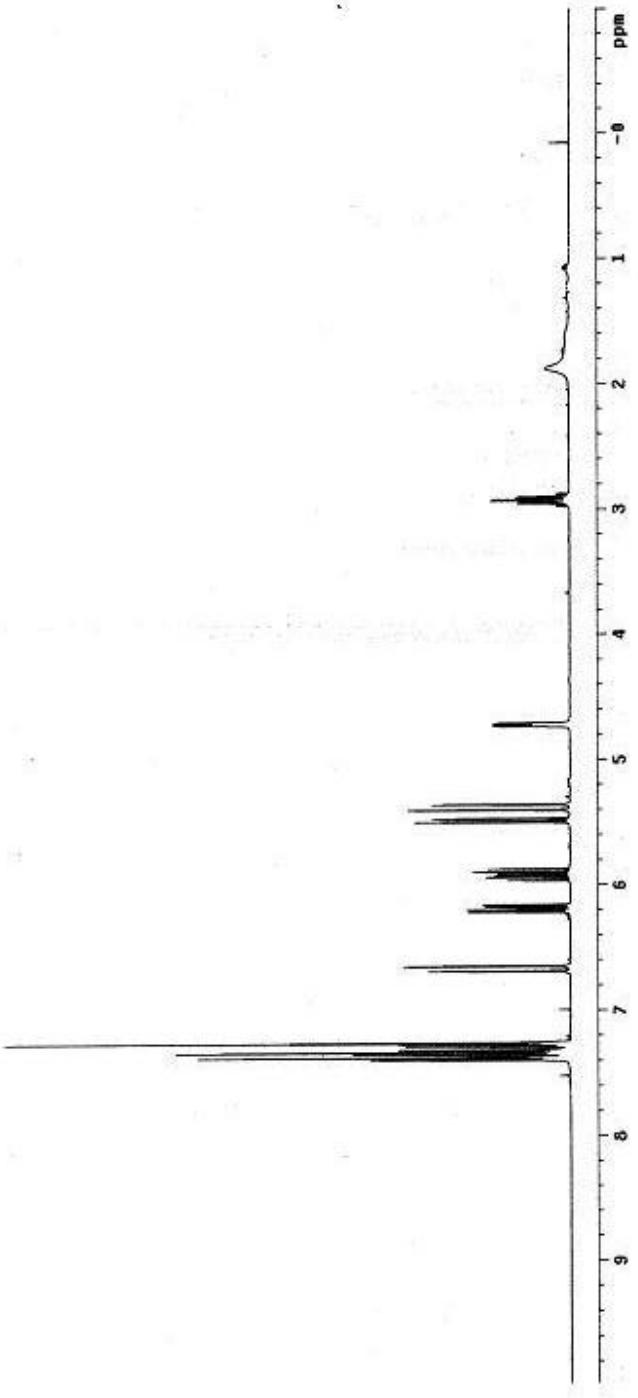
^{19}F NMR (376 MHz, $CDCl_3$): δ -67.31 (d, *J* = 10.0 Hz).

HPLC: (Chiralcel OB-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 254 nm), t_{major} = 7.0 min, t_{minor} = 7.8 min; ee = 87%.

[α]$_D^{25}$ = -23.64 (c =1.1, CH_2Cl_2).

FTIR (neat): 3426, 2953, 2896, 1626, 1494, 1455, 1386, 1247, 1196, 1153, 1089, 1050, 1028, 988, 906, 835, 786, 763, 718, 698 cm^{-1}.

HRMS (CI) Calcd. for $C_{13}H_{14}OF_3$ $[M+H]^+$: 243.0997, Found: 243.1000.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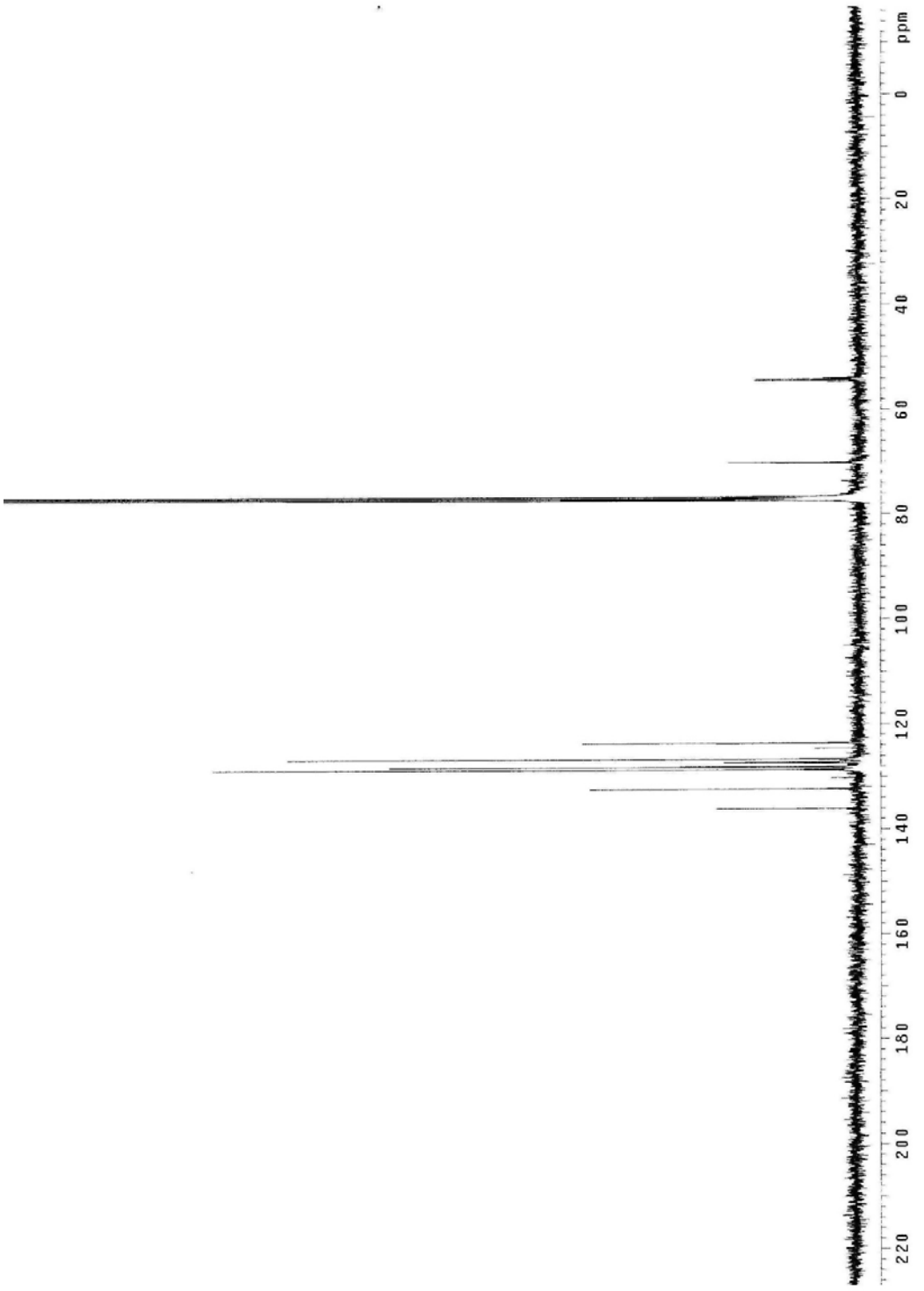
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160
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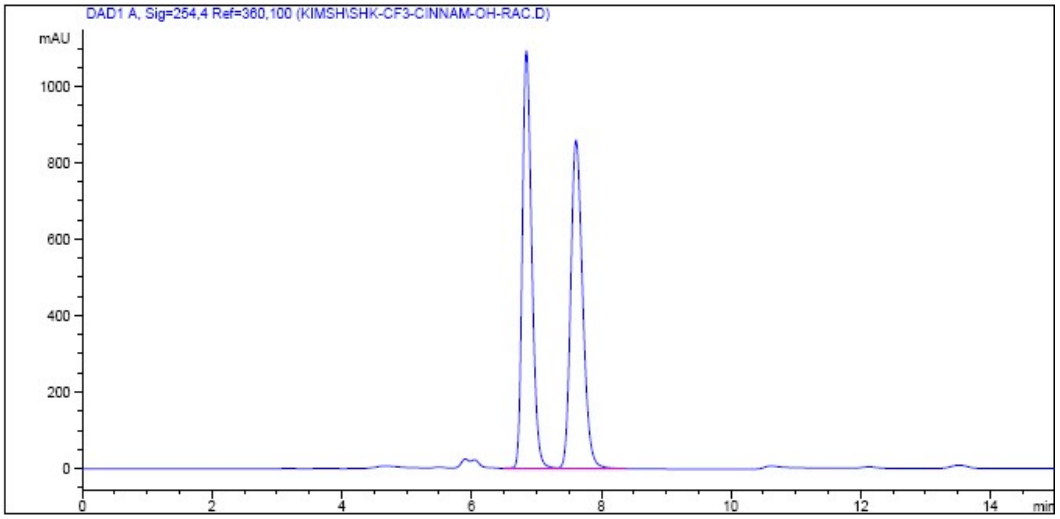
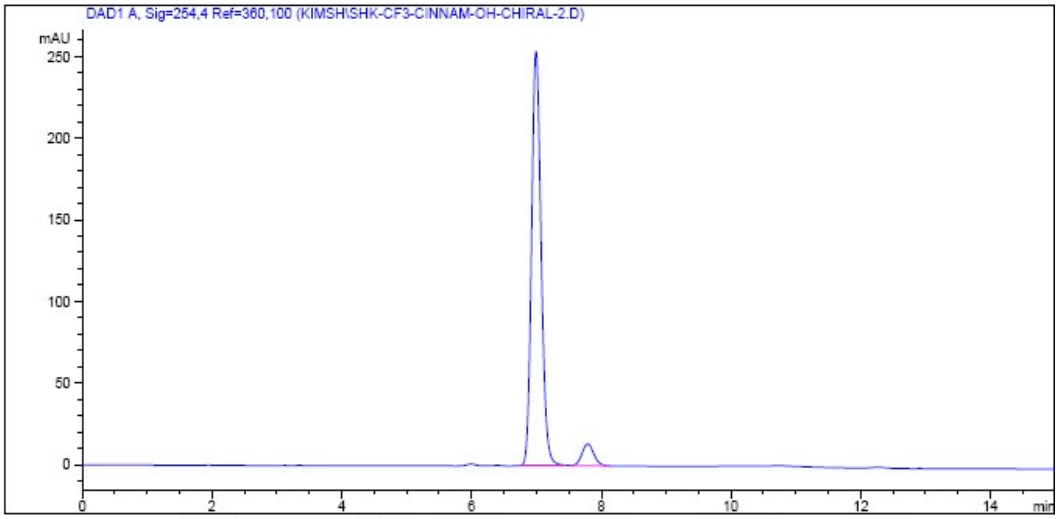
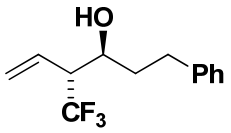


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.844	BV	0.1558	1.10525e4	1094.70068	50.0341
2	7.610	VB	0.1977	1.10375e4	860.45605	49.9659



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.992	BB	0.1575	2603.64795	254.27730	93.6994
2	7.789	BB	0.1993	175.07492	13.49796	6.3006

(*3S,4R*)-1-phenyl-4-(trifluoromethyl)hex-5-en-3-ol 3.3d



An oven-dried sealed tube under an atmosphere of N_2 was charged with 3-phenylpropan-1-ol **3.1d** (27.2 mg, 0.20 mmol, 100 mol%), (*R*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), Na_2CO_3 (21.2 mg, 0.20 mmol, 100 mol%). THF (1.0 mL, 0.2 M), H_2O (7.2 μL, 0.4 mmol, 200 mol%), and α-(trifluoromethyl)allyl benzoate (92.1 mg, 0.40 mmol, 200 mol%) were added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 with 0.1% TEA) provided **3.3d** (29.8 mg, 0.121 mmol) as a colorless oil in 61% yield (>20:1 dr).

TLC (SiO_2): R_f = 0.5 (ethyl acetate: hexanes, 1:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.28 (m, 2H), 7.22-7.18 (m, 3H), 5.88 (dt, *J* = 17.2, 10.4 Hz, 1H), 5.46 (d, *J* = 10.4 Hz, 1H), 5.34 (d, *J* = 17.2 Hz, 1H), 4.11-4.05 (m, 1H), 2.86-2.71 (m, 1H), 2.70-2.63 (m, 2H), 1.89-1.82 (m, 1H), 1.77-1.68 (m. 1H), 1.72 (d, *J* = 6.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.2, 128.5, 128.4, 127.2, 126.3 (q, *J* = 272.8 Hz), 126.1, 123.6, 68.1, 53.7 (q, *J* = 37.0 Hz), 36.5, 31.9.

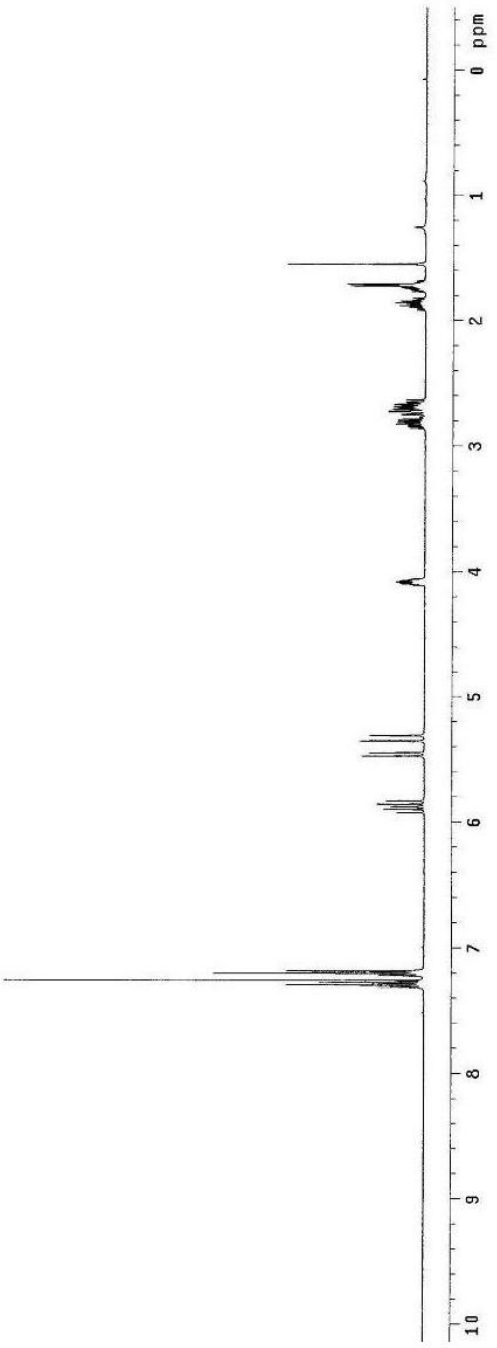
^{19}F NMR (376 MHz, $CDCl_3$): δ -67.61 (d, *J* = 9.8 Hz).

HPLC: (Chiralcel OB-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), t_{minor} = 5.8 min, t_{major} = 6.4 min; ee = 94%.

[α]$_D^{25}$ = -15.01 (c =0.4, CH_2Cl_2).

FTIR (neat): 3424, 3028, 2924, 2856, 1604, 1455, 1327, 1253, 1146, 1102, 998, 936, 749, 719, 699 cm^{-1}.

HRMS (CI) Calcd. for $C_{13}H_{16}OF_3$ $[M+H]^+$: 245.1155, Found: 245.1153.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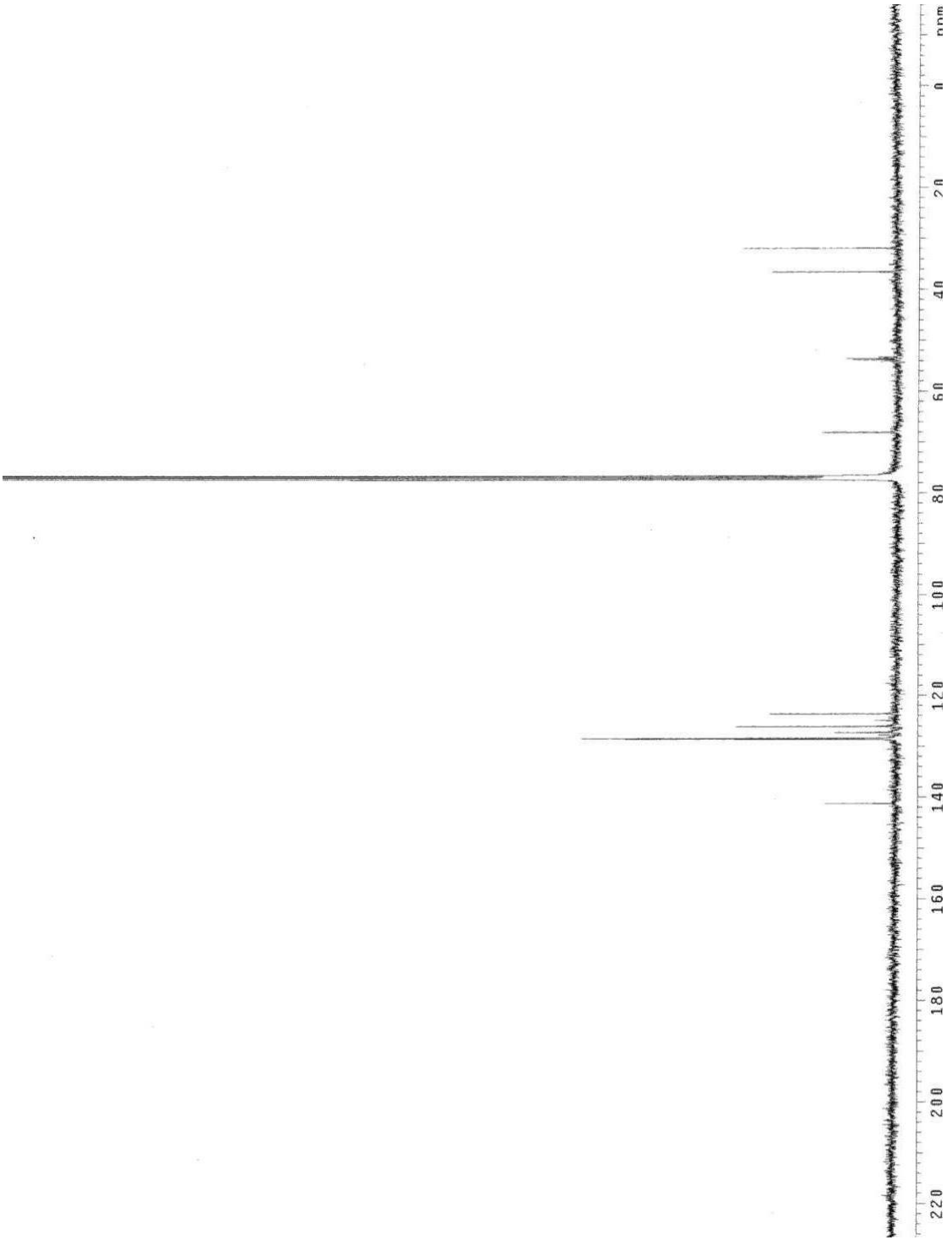
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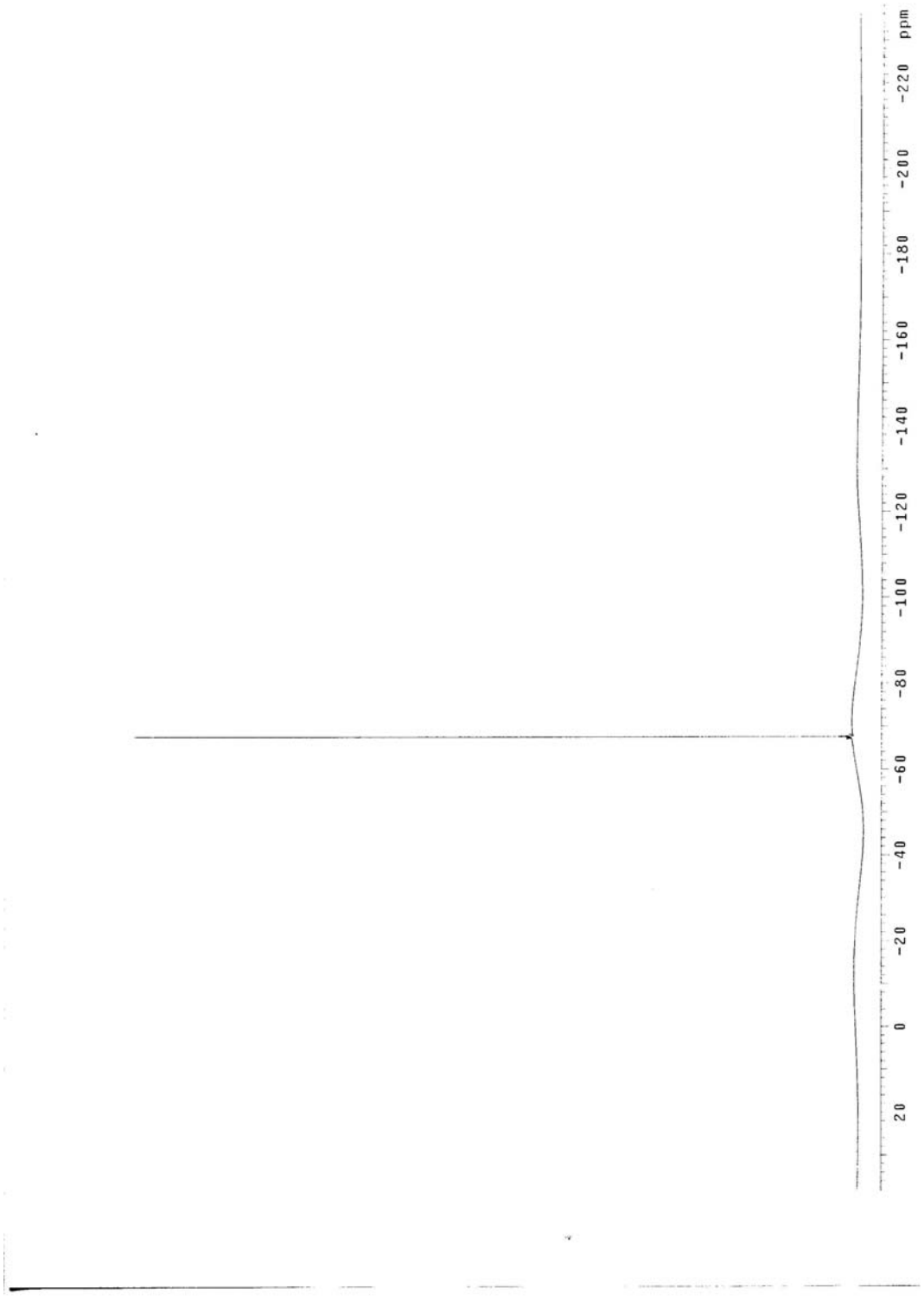
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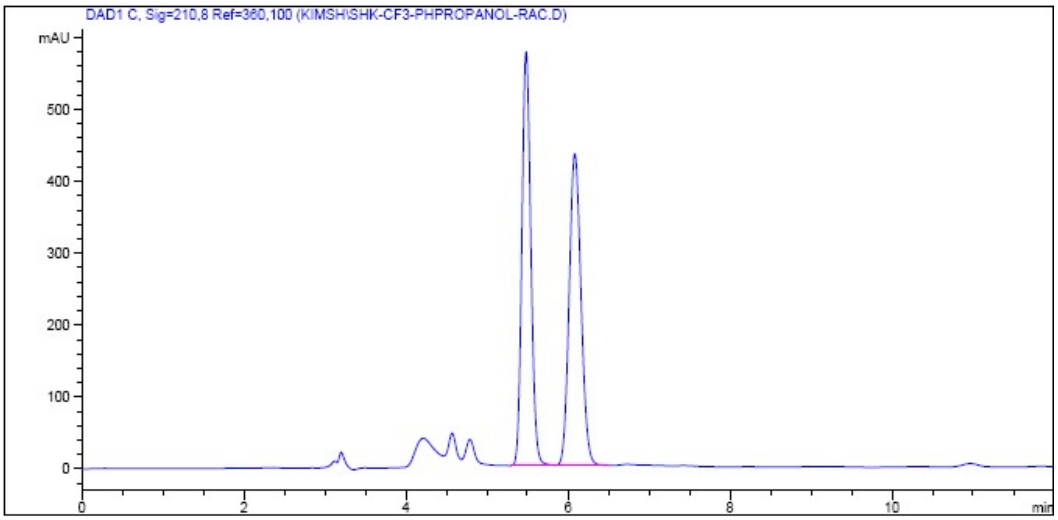
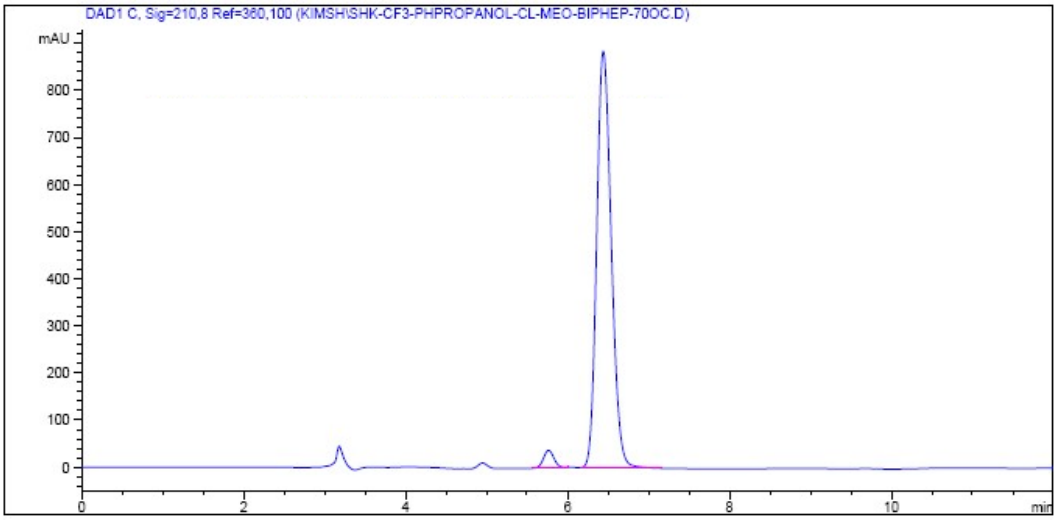
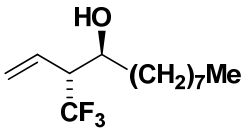


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.481	BV	0.1196	4424.38623	576.07074	50.0408
2	6.082	VB	0.1587	4417.17871	434.20898	49.9592



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.763	BB	0.1480	368.48840	38.39824	3.2050
2	6.439	BB	0.1965	1.11290e4	886.25195	96.7950

(*3R,4S*)-3-(trifluoromethyl)dodec-1-en-4-ol 3.3e



An oven-dried sealed tube under an atmosphere of N_2 was charged with nonan-1-ol **3.1e** (28.8 mg, 0.20 mmol, 100 mol%), (*R*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), Na_2CO_3 (21.2 mg, 0.20 mmol, 100 mol%). THF (1.0 mL, 0.2 M), H_2O (7.2 μL, 0.4 mmol, 200 mol%), and α-(trifluoromethyl)allyl benzoate (92.1 mg, 0.40 mmol, 200 mol%) were added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:15 with 0.1% TEA) provided **3.3e** (32.3 mg, 0.128 mmol) as a colorless oil in 64% yield (>10:1 dr).

TLC (SiO_2): R_f = 0.6 (ethyl acetate: hexanes, 1:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87 (dt, *J* = 17.6, 10.0 Hz, 1H), 5.46 (d, *J* = 10.0 Hz, 1H), 5.34 (d, *J* = 17.6 Hz, 1H), 4.07-4.04 (m, 1H), 2.71 (pd, *J* = 10.2, 2.4 Hz, 1H), 1.64 (d, *J* = 4.8 Hz, 1H), 1.57-1.27 (m, 14H), 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 127.3, 126.5 (q, *J* = 279.0 Hz), 123.4, 68.7, 53.4 (q, *J* = 24.5 Hz), 34.8, 31.8, 29.5, 29.4, 29.2, 25.5, 22.6, 14.1.

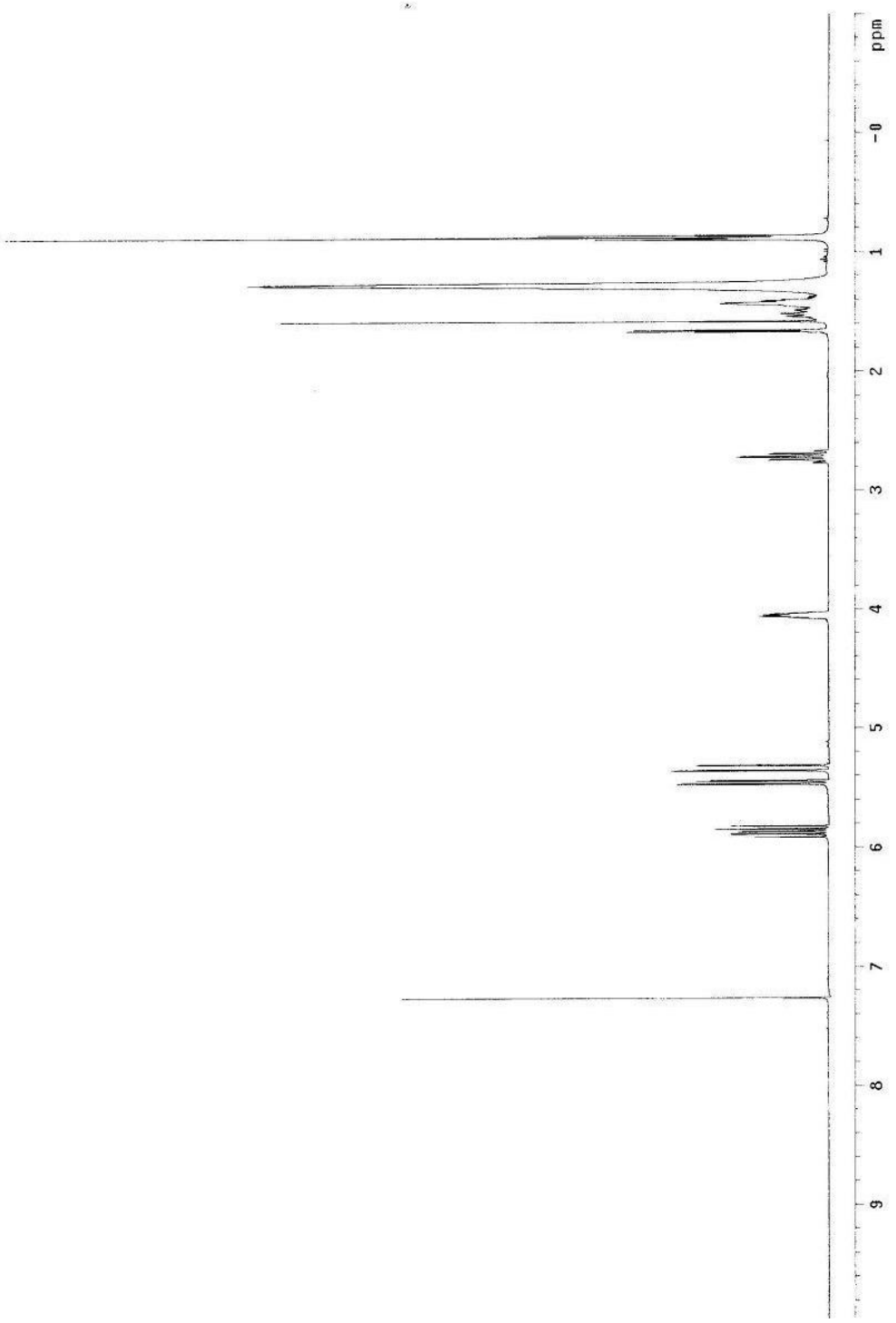
^{19}F NMR (376 MHz, $CDCl_3$): δ -67.72 (d, *J* = 10.4 Hz).

HPLC: Enantiomeric excess was determined by HPLC analysis of the 4-nitrobenzoate derivative of the product (Chiralcel OJ-H column, hexanes:*i*-PrOH = 99:1, 0.75 mL/min, 254 nm), t_{minor} = 28.4 min, t_{major} = 36.1 min; ee = 92%.

$[\alpha]_D^{25}$ = -29.29 (c =1.4, CH_2Cl_2).

FTIR (neat): 3463, 2955, 2924, 2854, 1716, 1624, 1465, 1378, 1246, 1167, 1103, 962, 740, 727, 640. cm^{-1}.

HRMS (CI) Calcd. for $C_{13}H_{22}OF_3$ $[M-H]^+$: 251.1621, Found: 251.1623.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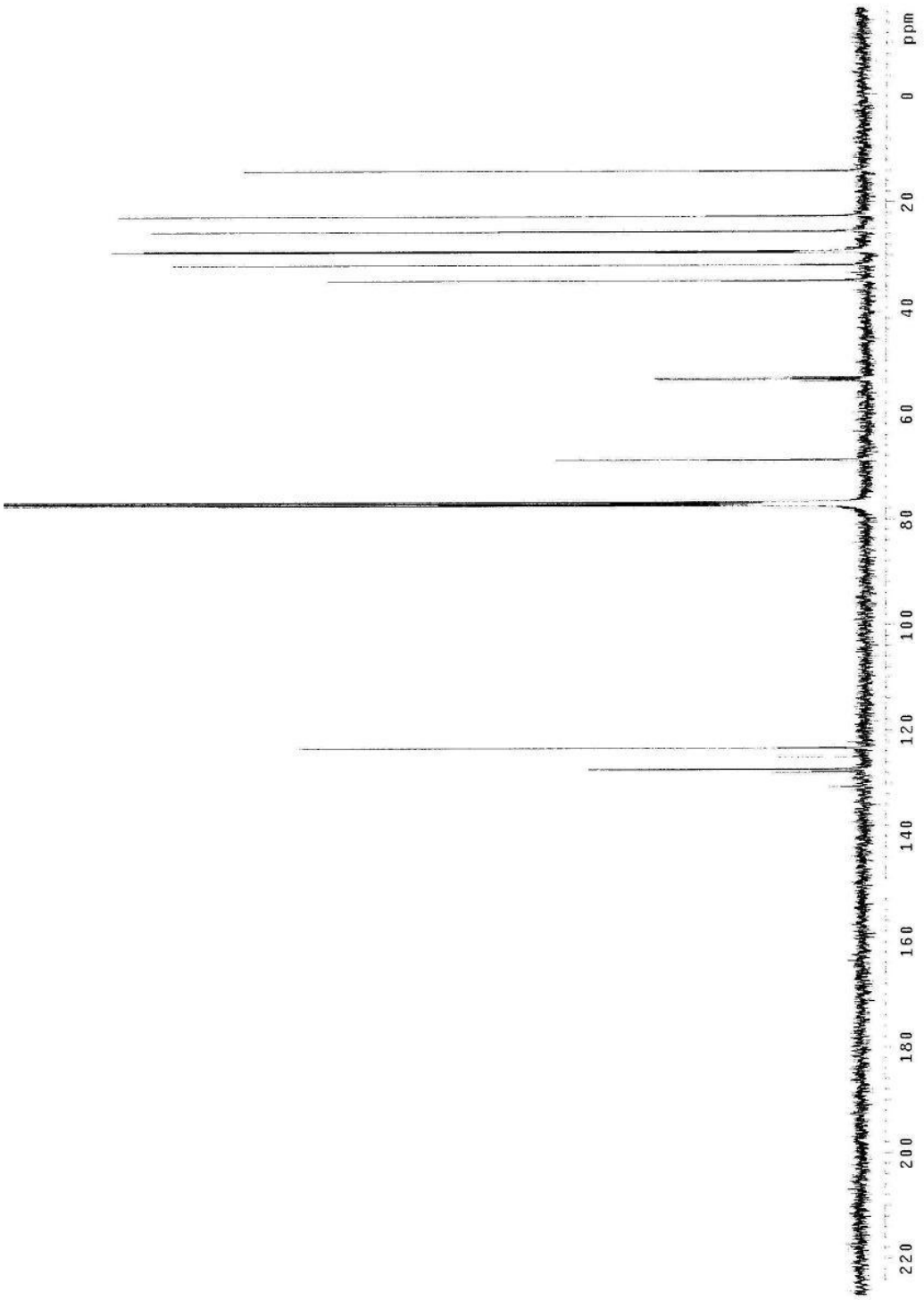
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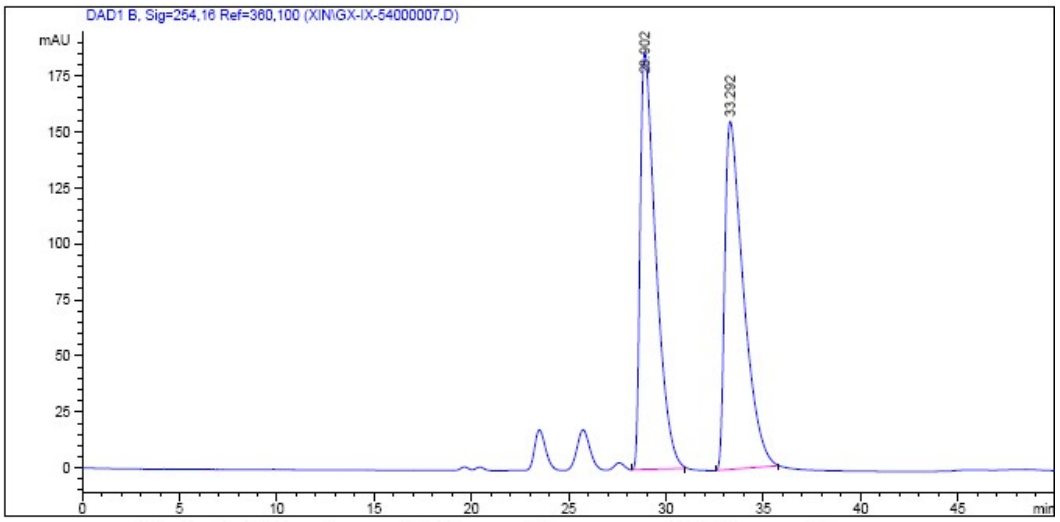
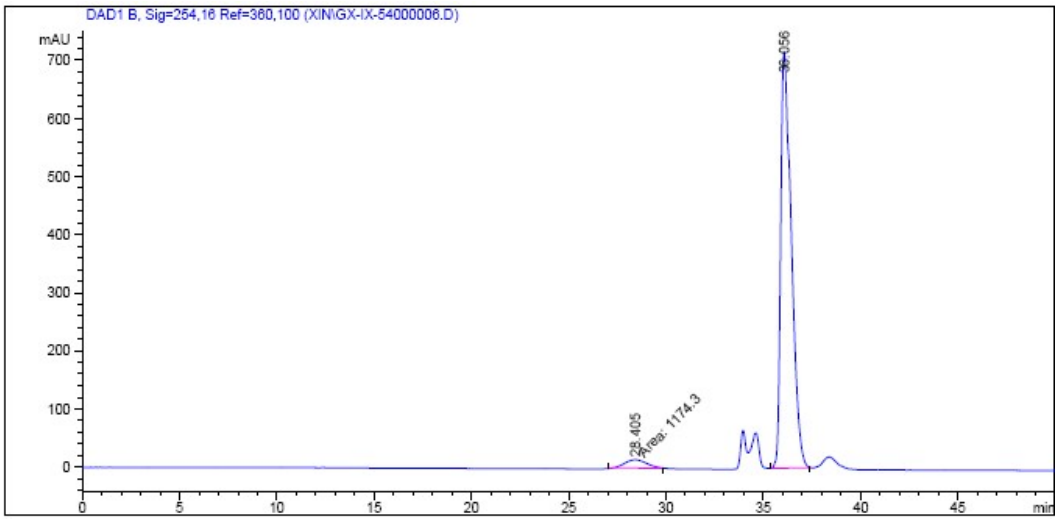
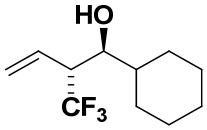


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.902	VB	0.8278	1.04637e4	186.15135	50.2064
2	33.292	BB	0.9714	1.03777e4	155.35107	49.7936



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.405	MM	1.3302	1174.30432	14.71362	4.1369
2	36.056	BB	0.5409	2.72119e4	716.75745	95.8631

(*1S,2R*)-1-cyclohexyl-2-(trifluoromethyl)but-3-en-1-ol 3.3f[14]



An oven-dried sealed tube under an atmosphere of N_2 was charged with cyclohexylmethanol **3.1f** (22.8 mg, 0.20 mmol, 100 mol%), (*R*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%), and α-(trifluoromethyl)allyl benzoate (92 mg, 0.40 mmol, 200 mol%) were added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **3.3f** (38.9 mg, 0.154 mmol) as a colorless oil in 77% yield.

TLC (SiO_2): R_f = 0.6 (ethyl acetate:hexanes, 1:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89 (dt, *J* = 17.2, 10.4 Hz, 1H), 5.44 (d, *J* = 10.4 Hz, 1H), 5.45 (d, *J* = 17.2 Hz, 1H), 3.73-3.69 (m, 1H), 2.94 (pd, *J* = 9.6, 2.4 Hz, 1H), 1.78-0.94 (m, 11H). *To corroborate the assignement of relative stereochemistry, the chemical shift and coupling constant were correlated with a known compound.*

^{13}C NMR (100 MHz, $CDCl_3$): δ 127.4, 126.7 (q, *J* = 279.8 Hz), 123.1, 72.9, 50.3 (q, *J* = 23.8 Hz), 40.4, 28.8, 28.8, 26.2, 25.8, 25.6.

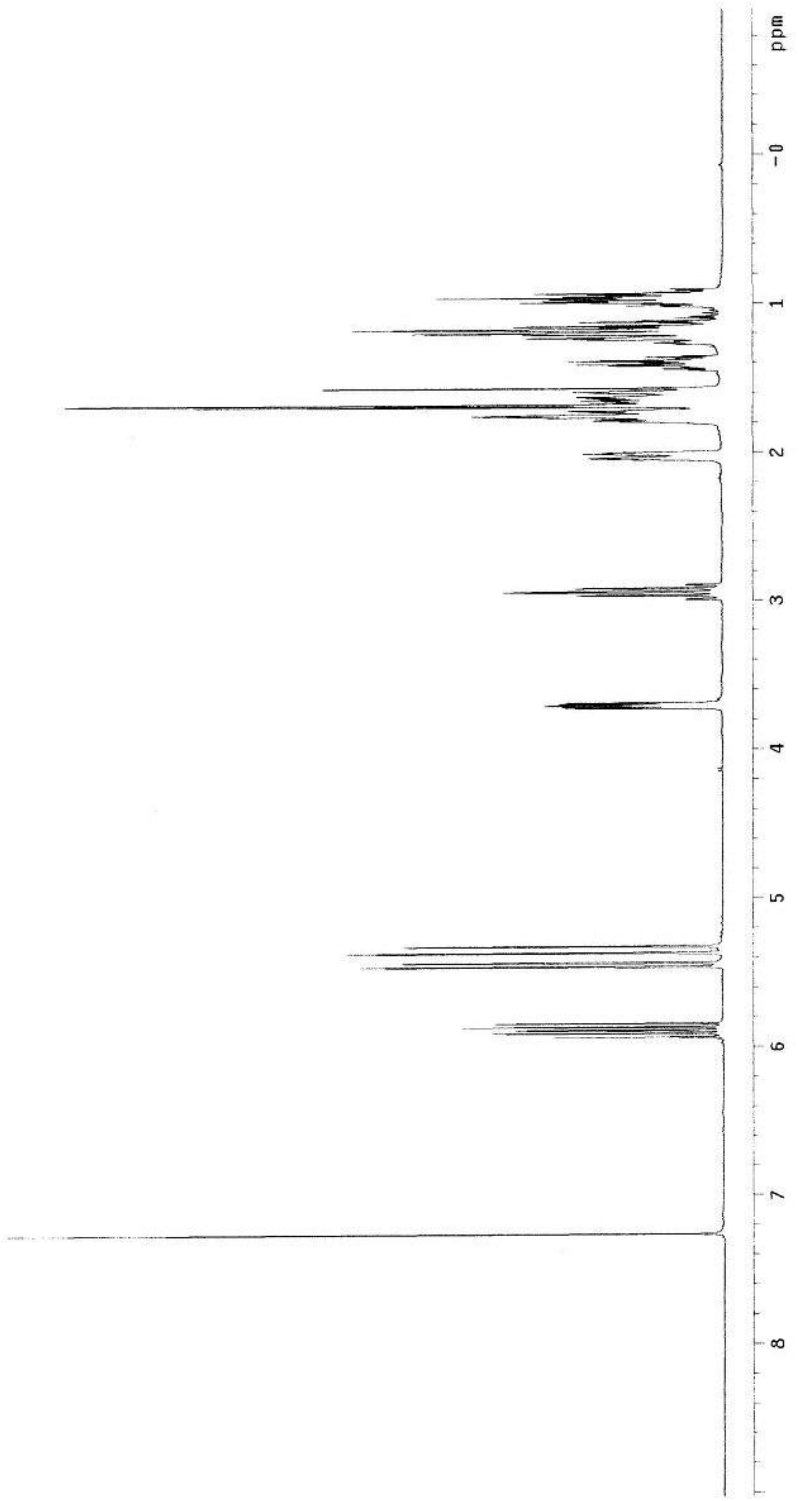
^{19}F NMR (376 MHz, $CDCl_3$): δ -67.63 (d, *J* = 9.8 Hz).

HPLC: Enantiomeric excess was determined by HPLC analysis of the 4-nitrobenzoate derivative of the product (Chiralcel OJ-H column, hexanes:*i*-PrOH = 98:2, 0.75 mL/min, 254 nm), t_{minor} = 6.8 min, t_{major} = 7.6 min; ee = 91%.

$[\alpha]_D^{25}$ = -27.35 (c =1.7, CH_2Cl_2).

FTIR (neat): 3410, 2926, 2854, 1451, 1328, 1257, 1145, 1103, 962, 744, 720 cm^{-1}.

HRMS (CI) Calcd. for $C_{11}H_{18}OF_3$ $[M+H]^+$: 223.1310, Found: 223.1304.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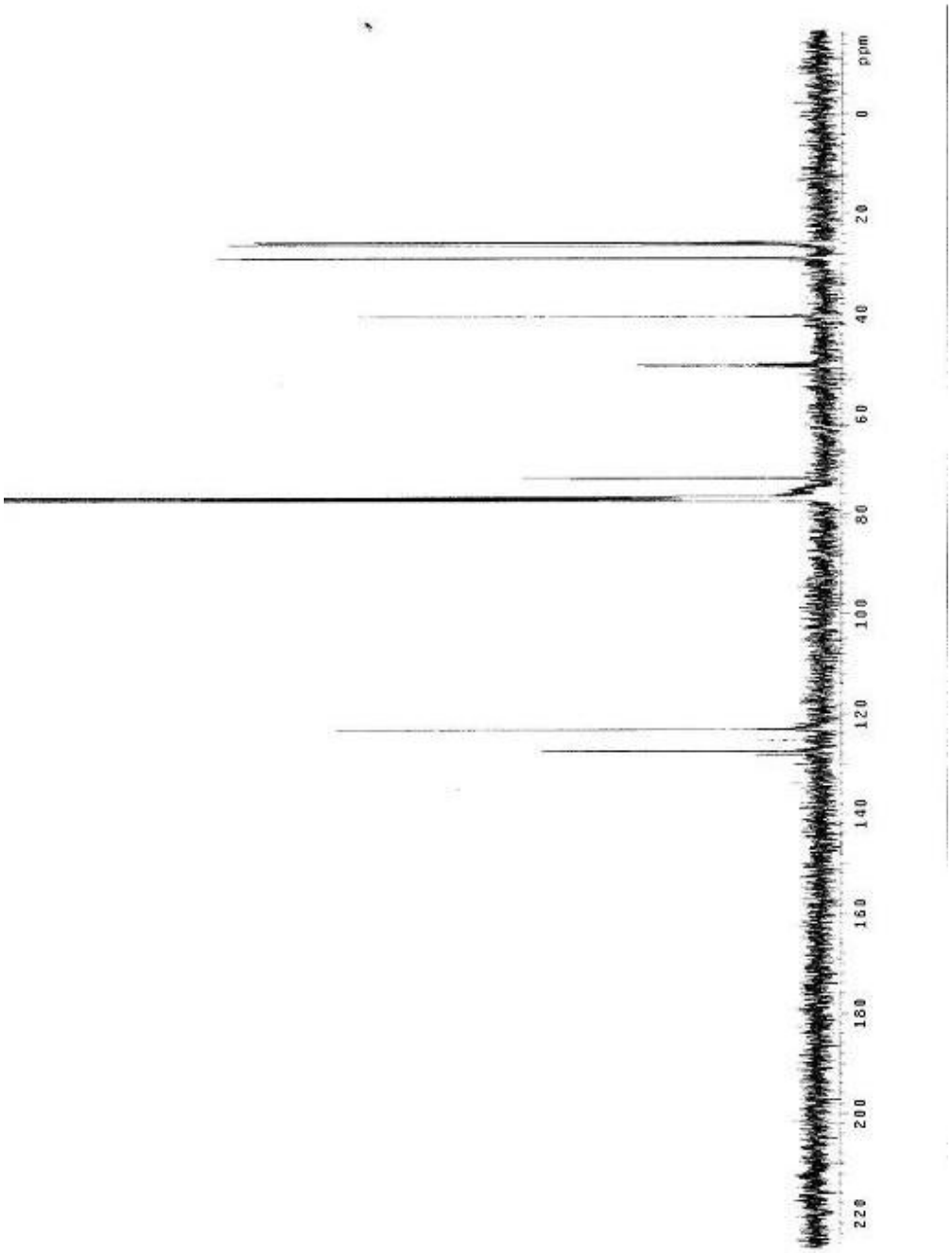
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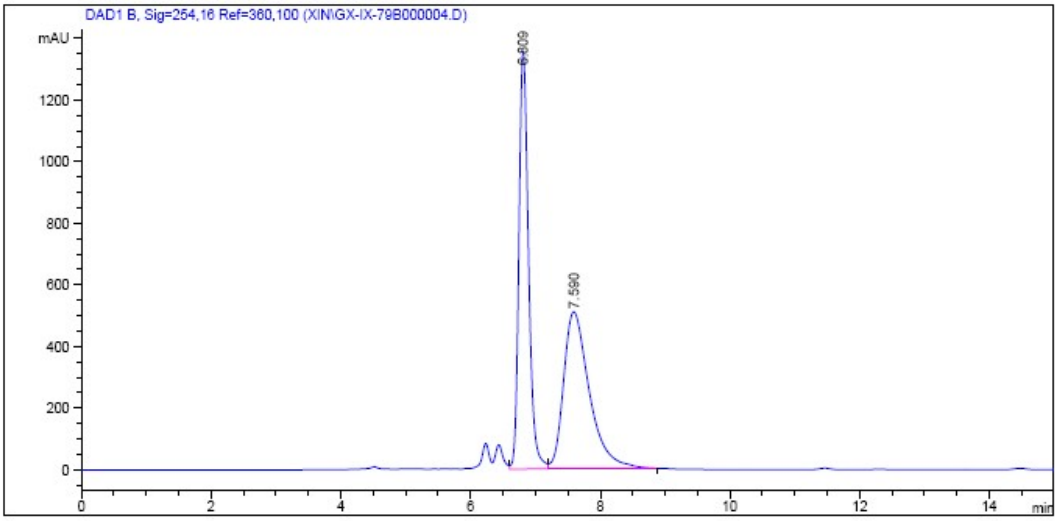
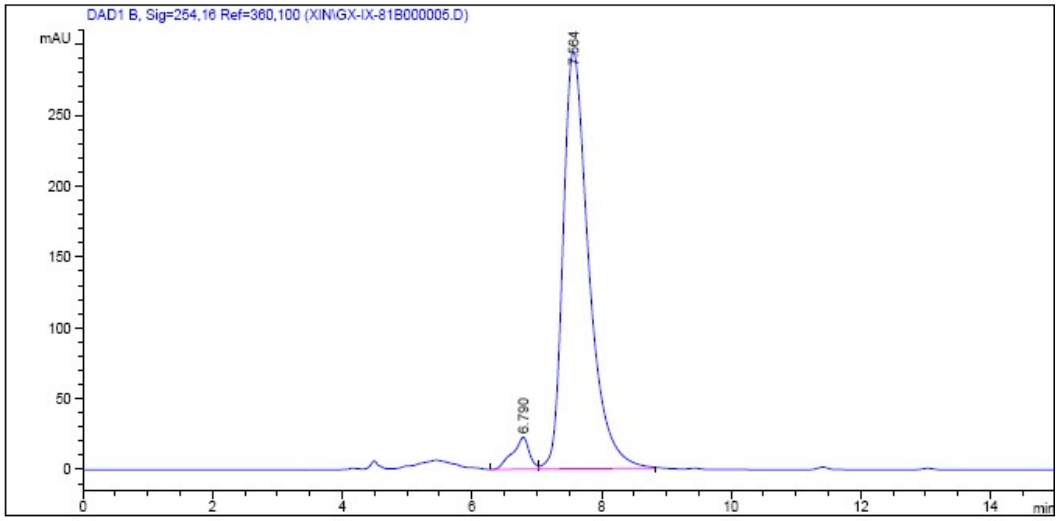
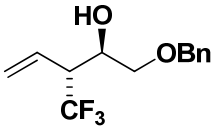


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.809	VV	0.1562	1.40018e4	1358.97339	49.5781
2	7.590	VB	0.4209	1.42401e4	511.36313	50.4219



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.790	VV	0.2493	409.54404	22.61721	4.8028
2	7.564	VB	0.4173	8117.72656	294.79523	95.1972

(*2R,3R*)-1-(benzyloxy)-3-(trifluoromethyl)pent-4-en-2-ol 3.3g



An oven-dried sealed tube under an atmosphere of N_2 was charged with 2-(benzyloxy)ethanol **3.1g** (30.4 mg, 0.20 mmol, 100 mol%), (*R*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), Na_2CO_3 (21.2 mg, 0.20 mmol, 100 mol%). THF (1.0 mL, 0.2 M), H_2O (7.2 μL, 0.4 mmol, 200 mol%), and α-(trifluoromethyl)allyl benzoate (92.1 mg, 0.40 mmol, 200 mol%) were added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 with 0.1% TEA) provided **3.3g** (29.7 mg, 0.114 mmol) as a colorless oil in 57% yield (>20:1 dr).

TLC (SiO_2): R_f = 0.4 (ethyl acetate: hexanes, 1:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.29 (m, 5H), 5.88 (dt, *J* = 17.2, 9.6 Hz, 1H), 5.42 (d, *J* = 9.6 Hz, 1H), 5.40 (d, *J* = 17.2 Hz, 1H), 4.58-4.51 (m, 2H), 4.28-4.24 (m, 1H), 3.46 (d, *J* = 5.6 Hz, 2H), 2.91 (pd, *J* = 10.6, 2.8 Hz, 1H), 2.24 (br, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 128.5, 128.0, 127.8, 127.3, 126.2 (q, *J* = 278.3 Hz), 123.4, 73.4, 71.4, 67.2, 50.5 (q, *J* = 26.0 Hz).

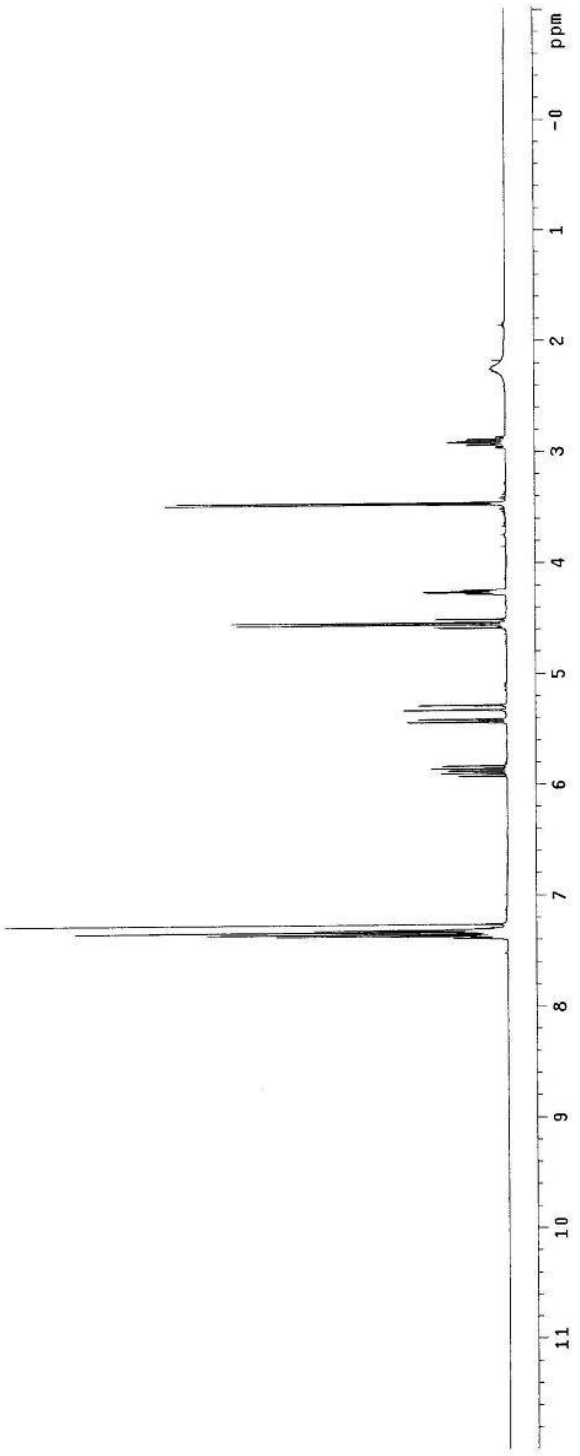
^{19}F NMR (376 MHz, $CDCl_3$): δ -67.83 (d, *J* = 10.0 Hz).

HPLC: (Chiralcel OB-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), t_{major} = 8.3 min, t_{minor} = 11.8 min; ee = 99%.

[α]$_D^{25}$ = -10.67 (c =1.5, CH_2Cl_2).

FTIR (neat): 3454, 2919, 2851, 1454, 1258, 1097, 908, 730, 697 cm^{-1}.

HRMS (CI) Calcd. for $C_{13}H_{15}O_2F_3$ $[M]^+$: 260.1024, Found: 260.1023.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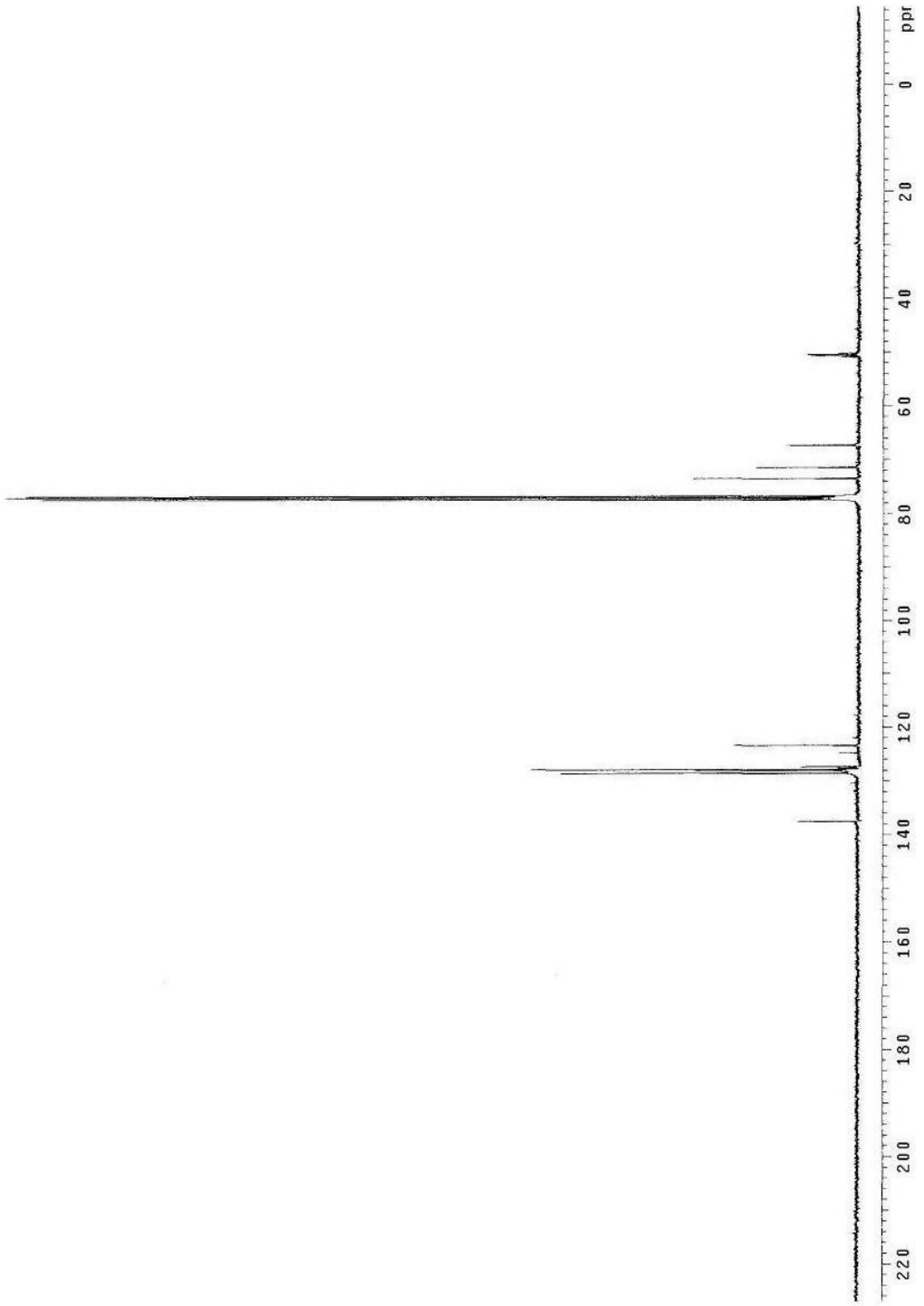
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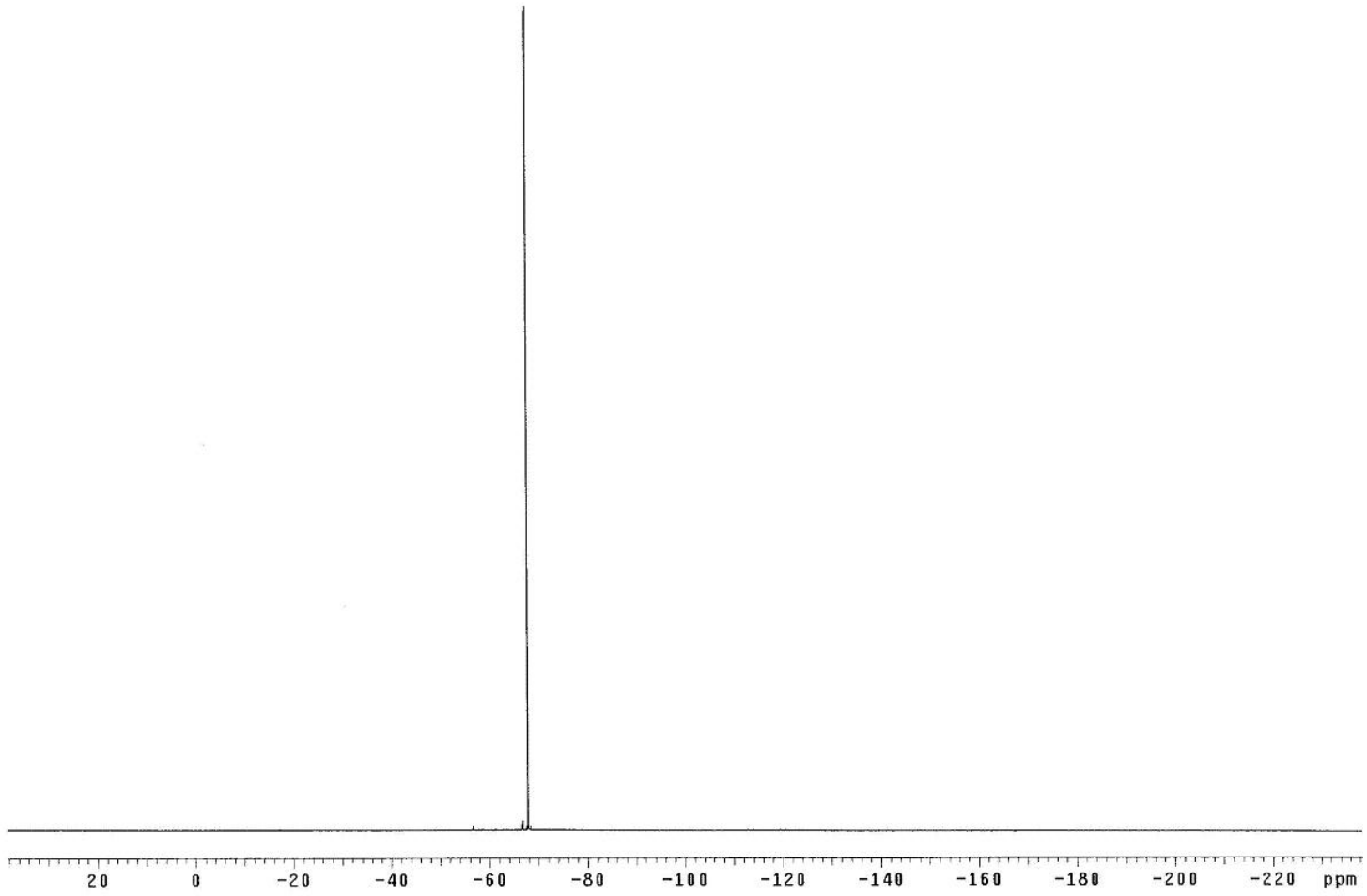
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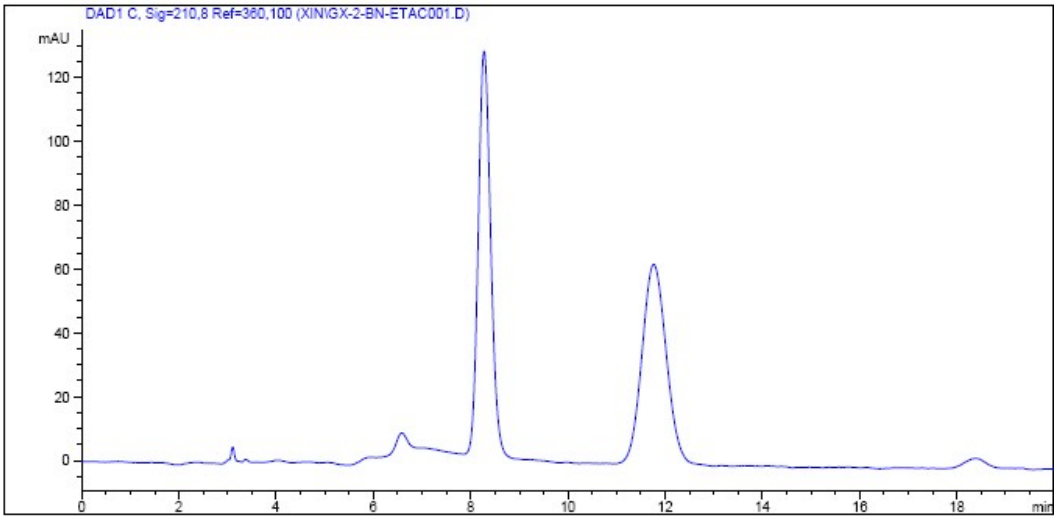

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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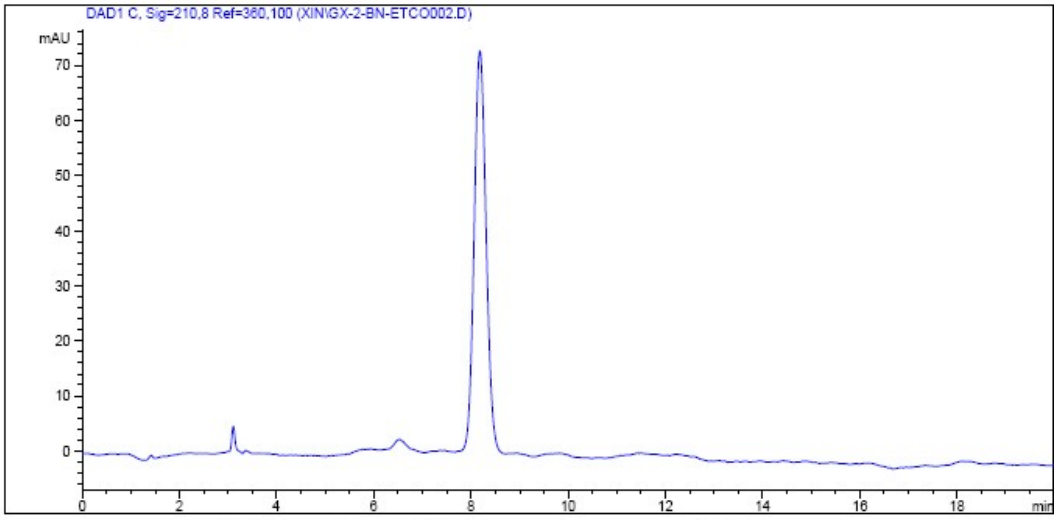
2	11.761	BB	0.5348	2172.09570	62.59485	49.0996



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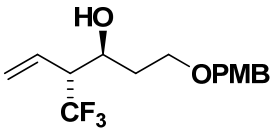
1	8.179	BB	0.2653	1245.89783	72.92858	100.0000

(*3S,4R*)-1-(4-methoxybenzyloxy)-4-(trifluoromethyl)hex-5-en-3-ol 3.3h



An oven-dried sealed tube under an atmosphere of N_2 was charged with 3-(4-methoxybenzyloxy)propan-1-ol **3.1h** (39.2 mg, 0.20 mmol, 100 mol%), (*R*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), Na_2CO_3 (21.2 mg, 0.20 mmol, 100 mol%). THF (1.0 mL, 0.2 M), H_2O (7.2 μL, 0.4 mmol, 200 mol%), and α-(trifluoromethyl)allyl benzoate (92.1 mg, 0.40 mmol, 200 mol%) were added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 with 0.1% TEA) provided **3.3h** (38.4 mg, 0.126 mmol) as a colorless oil in 63% yield (10:1 dr).

TLC (SiO_2): R_f = 0.4 (ethyl acetate: hexanes, 1:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.22 (m, 2H), 6.90-6.86 (m, 2H), 5.91 (dt, *J* = 17.2, 10.0 Hz, 1H), 5.42 (d, *J* = 10.0 Hz, 1H), 5.30 (d, *J* = 17.2 Hz, 1H), 4.44 (s, 2H), 4.31-4.27 (m, 1H), 3.80 (s, 3H), 3.72-3.60 (m, 2H), 3.00 (d, *J* = 2.4, 1H), 2.68 (pd, *J* = 9.6, 2.8 Hz, 1H), 1.92-1.82 (m, 1H), 1.66-1.59 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 129.7, 129.4, 127.8, 126.2 (q, *J* = 279.1 Hz), 123.0, 113.9, 73.1, 68.2, 68.1, 55.3, 53.8 (q, *J* = 25.3 Hz), 34.4.

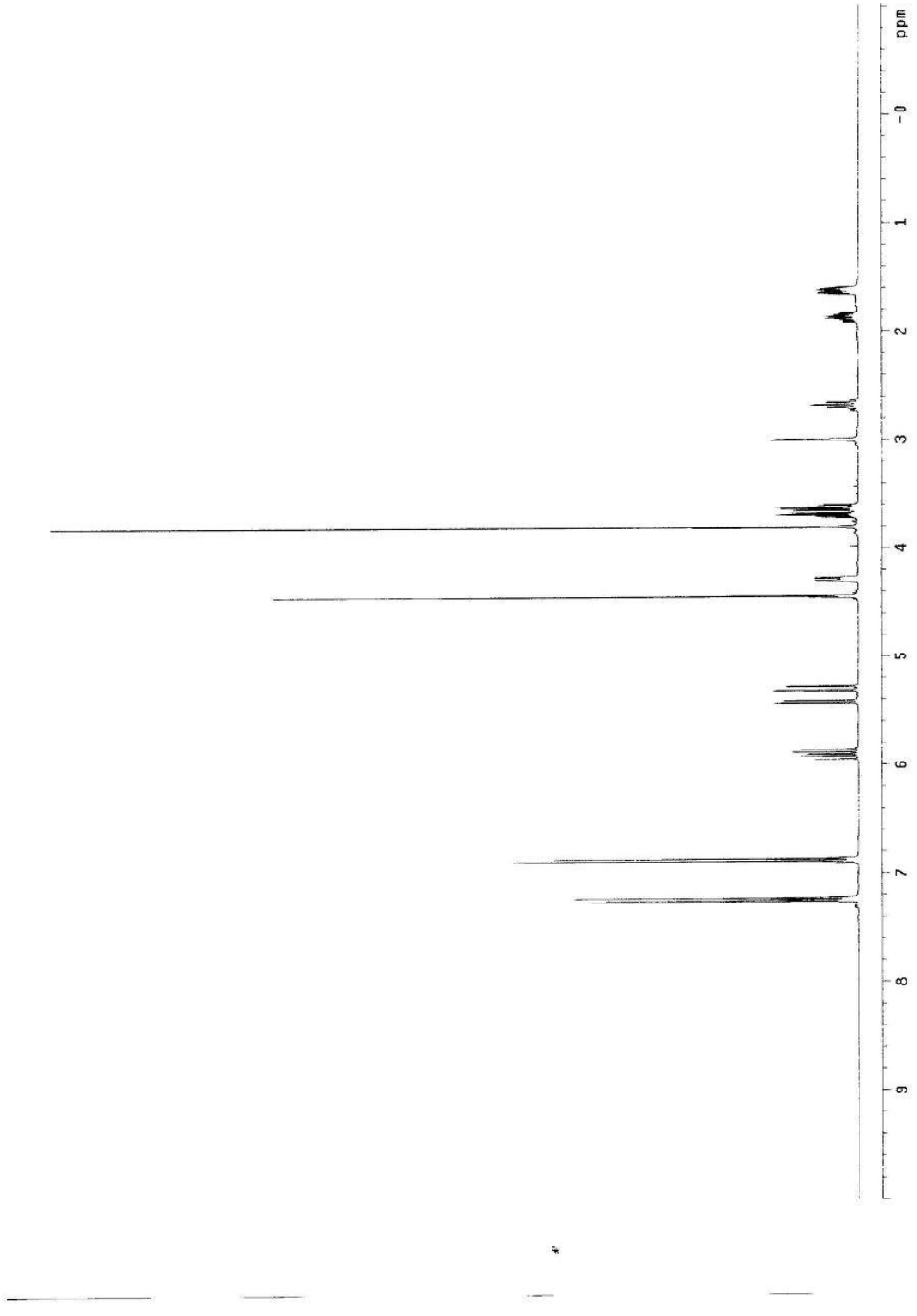
^{19}F NMR (376 MHz, $CDCl_3$): δ -67.70 (d, *J* = 10.2 Hz).

HPLC: (Chiralcel OB-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 230 nm), t_{major} = 14.4 min, t_{minor} = 21.1 min; ee = 94%.

[α]$_D^{25}$ = -22.50 (c =2.0, CH_2Cl_2).

FTIR (neat): 3486, 2935, 2868, 1513, 1250, 1173, 1096, 1033, 819 cm^{-1}.

HRMS (CI) Calcd. for $C_{15}H_{19}O_3F_3$ $[M]^+$: 304.1286, Found: 304.1287.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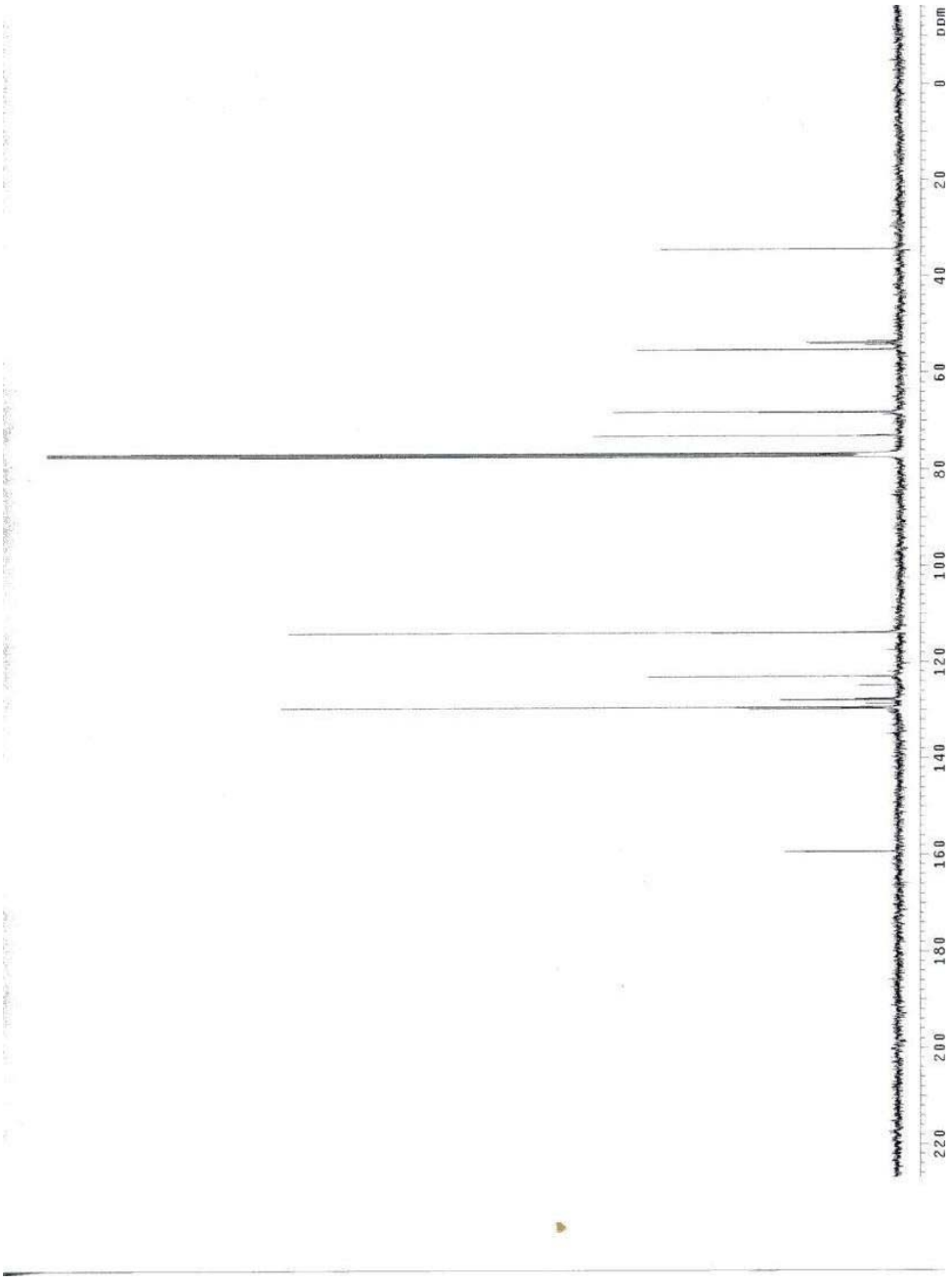
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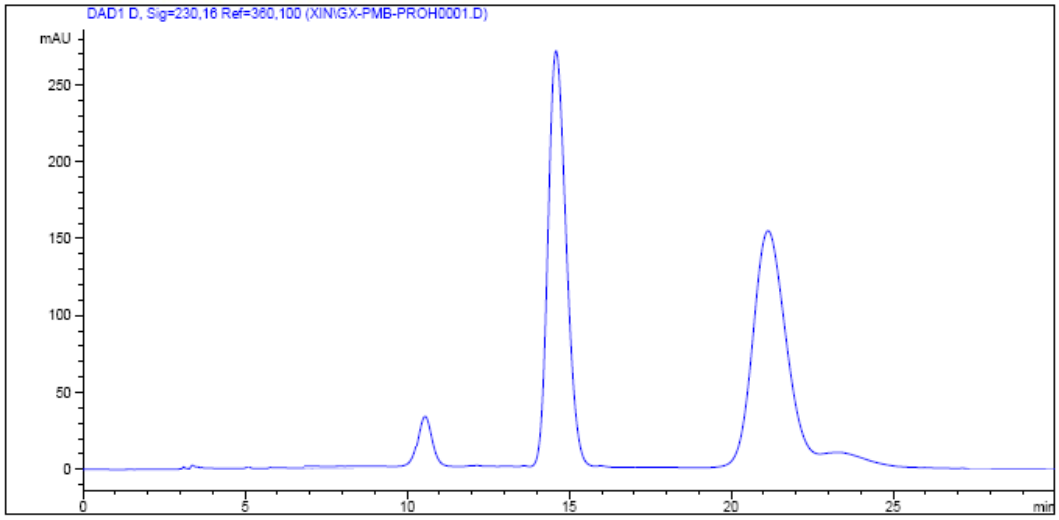
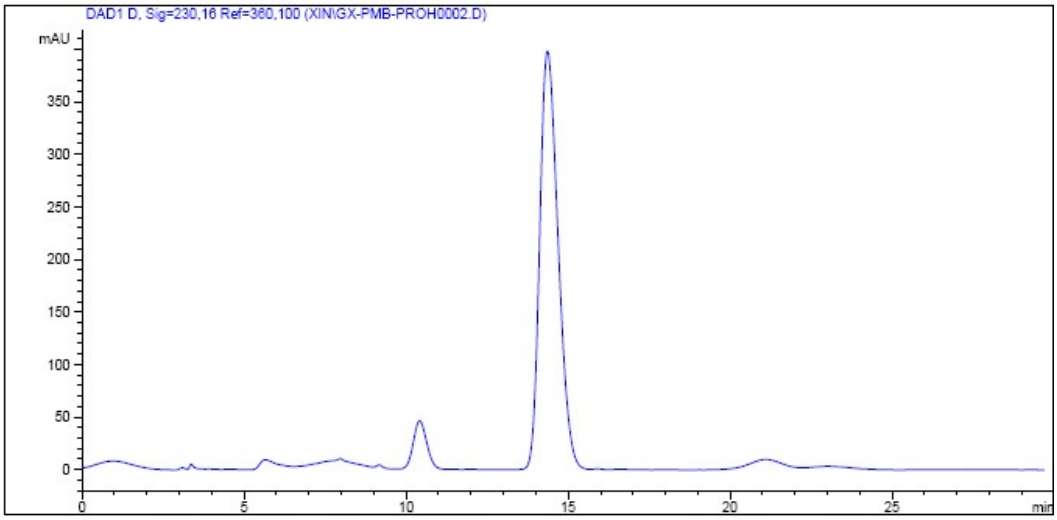
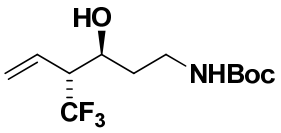


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.588	VB	0.6070	1.05001e4	270.40308	50.8452
2	21.131	BB	1.0598	1.01510e4	149.57124	49.1548



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.358	BB	0.6110	1.56619e4	398.09842	97.1108
2	21.099	BB	0.7132	465.96524	7.95743	2.8892

***tert*-butyl (*3S,4R*)-3-hydroxy-4-(trifluoromethyl)hex-5-enylcarbamate 3.3i**



An oven-dried sealed tube under an atmosphere of N_2 was charged with *tert*-butyl 3-hydroxypropylcarbamate **3.1i** (175.2 mg, 1.0 mmol, 100 mol%), (*R*)-**I** (51.5 mg, 0.05 mmol, 5 mol%), K_3PO_4 (215 mg, 1.0 mmol, 100 mol%). THF (1.0 mL, 1.0 M), H_2O (90 μL, 5.0 mmol, 500 mol%), and α-(trifluoromethyl)allyl benzoate (460 mg, 2.0 mmol, 200 mol%) were added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 with 0.1% TEA) provided **3.3i** (206.8 mg, 0.730 mmol) as a colorless oil in 73% yield.

TLC (SiO_2): R_f = 0.5 (ethyl acetate:hexanes, 1:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 (dt, *J* = 17.2, 10.0 Hz, 1H), 5.44 (d, *J* = 10.0 Hz, 1H), 5.32 (d, *J* = 17.2 Hz, 1H), 4.79 (br, 1H), 4.09 (d, *J* = 10.8 Hz, 1H), 3.49-3.42 (m, 1H), 3.36 (br, 1H), 3.14-3.08 (m, 1H), 2.67 (pd, *J* = 10.6, 2.8 Hz, 1H), 1.69-1.60 (m, 1H), 1.59-1.43 (m, 1H), 1.44 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 127.8, 126.2 (q, *J* = 279 Hz), 123.2, 79.9, 65.5, 53.8 (q, *J* = 25.3 Hz), 36.8, 35.8, 28.3.

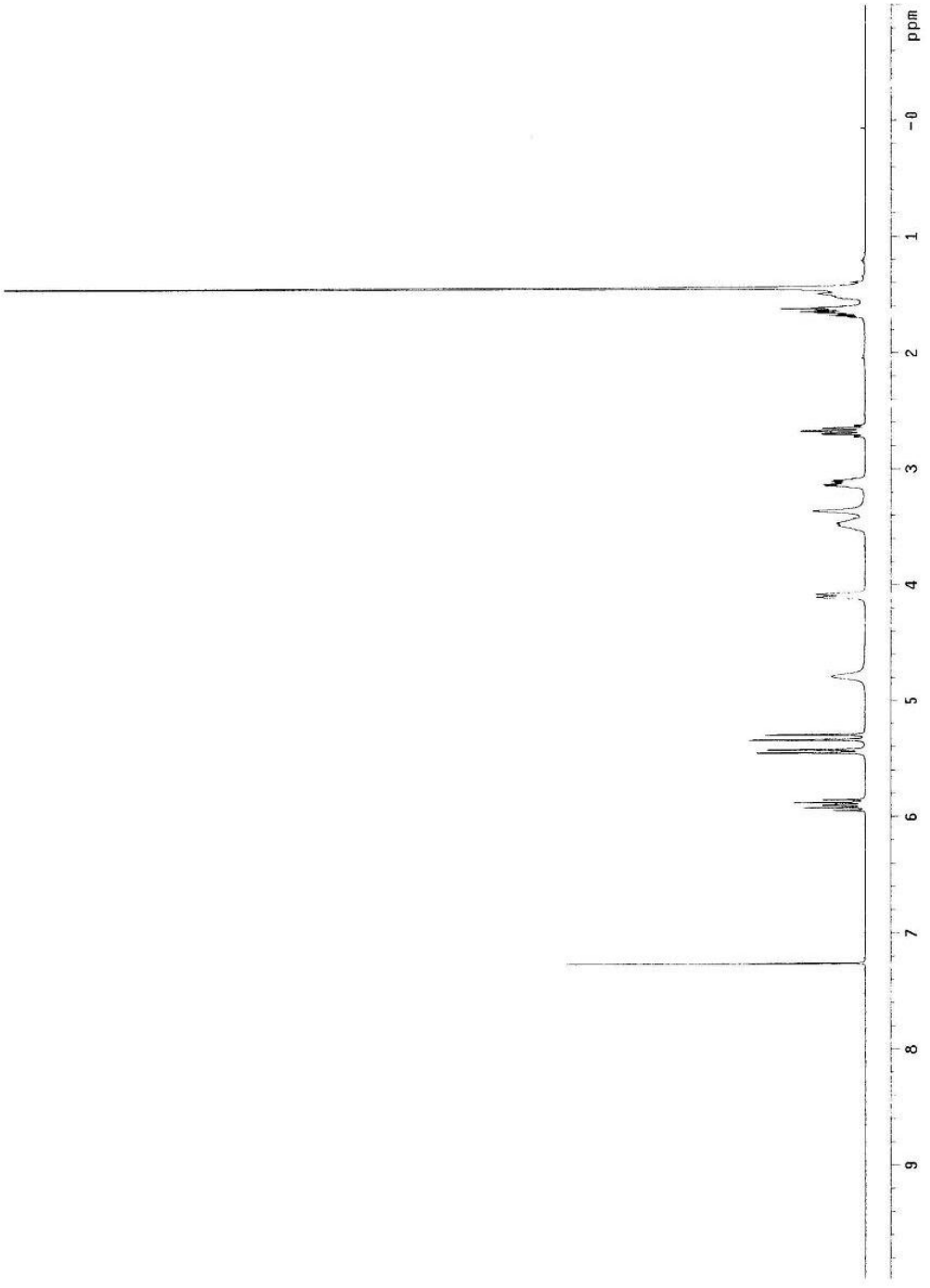
^{19}F NMR (376 MHz, $CDCl_3$): δ -67.88 (d, *J* = 10.3 Hz).

HPLC: Enantiomeric excess was determined by HPLC analysis of the 4-nitrobenzoate derivative of the product (Chiralcel OJ-H column, hexanes:*i*-PrOH = 98:2, 0.75 mL/min, 254 nm), t_{major} = 20.5 min, t_{minor} = 24.8 min; ee = 96%.

$[\alpha]_D^{25}$ = -7.14 (c =1.4, CH_2Cl_2).

FTIR (neat): 3350, 2925, 1682, 1517, 1367, 1252, 1169, 1147, 1105, 934, 861, 719 cm^{-1}.

HRMS (CI) Calcd. for $C_{12}H_{20}OF_3Na$ $[M+Na]^+$: 306.1290, Found: 306.1289.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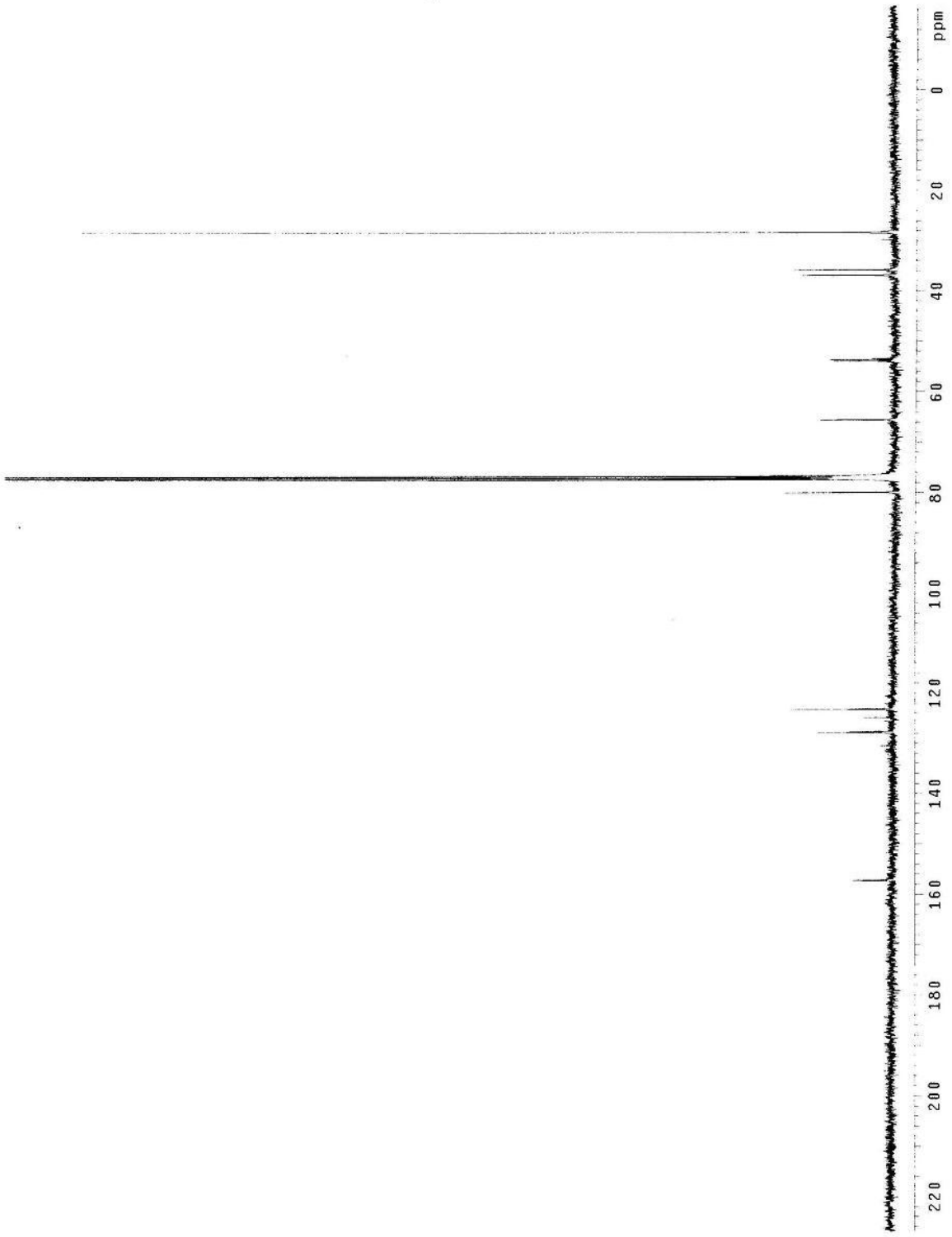
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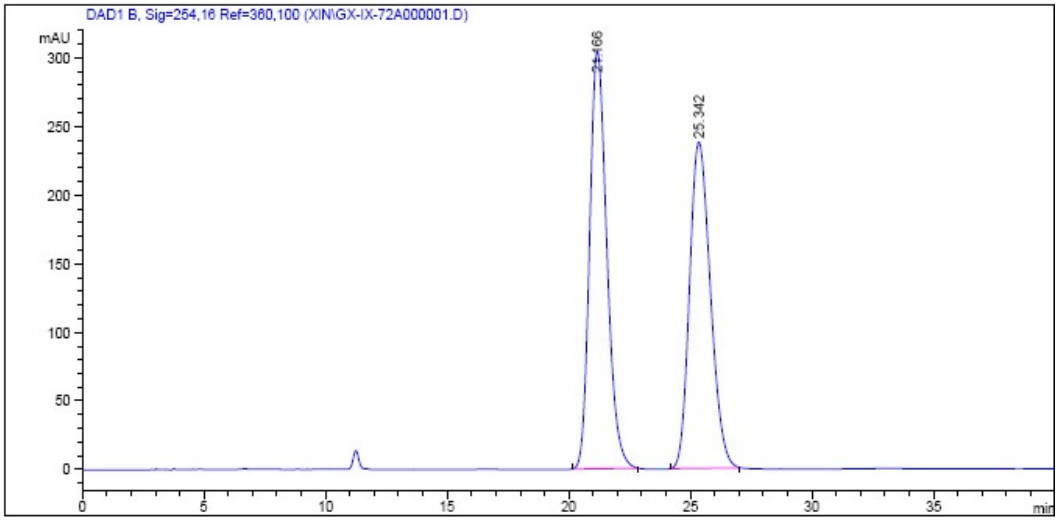
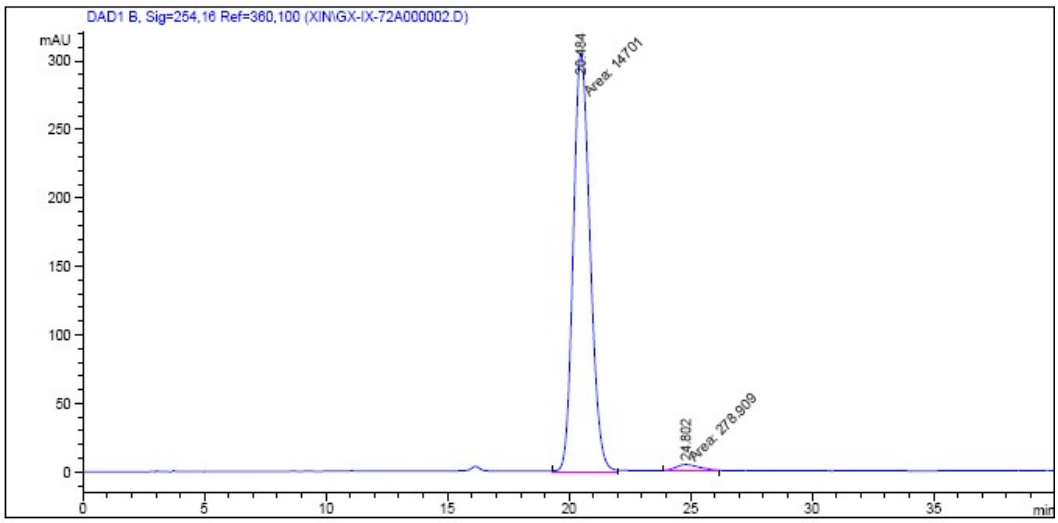
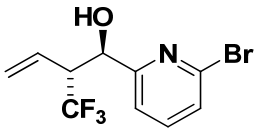


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.166	BB	0.7619	1.49681e4	304.26678	51.3535
2	25.342	BB	0.9301	1.41791e4	237.63631	48.6465



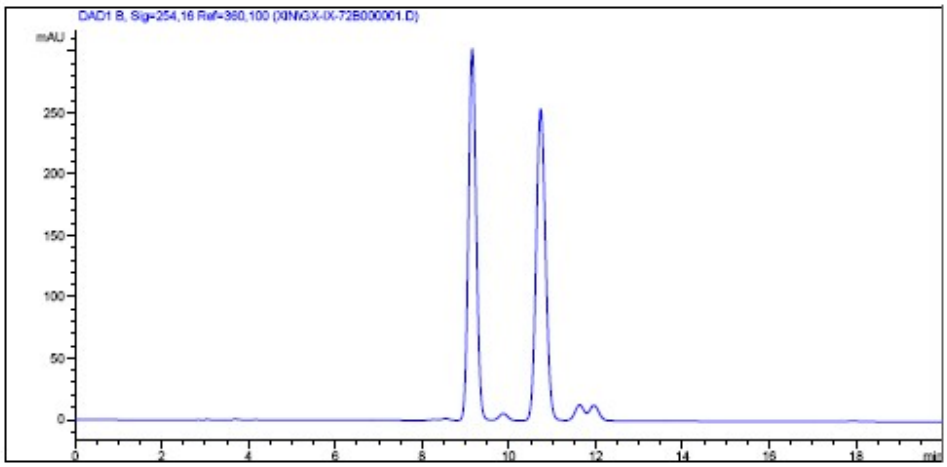
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.484	MF	0.8012	1.47010e4	305.80890	98.1381
2	24.802	MM	1.0948	278.90945	4.24592	1.8619

(*1R,2R*)-1-(6-bromopyridin-2-yl)-2-(trifluoromethyl)but-3-en-1-ol 3.3a

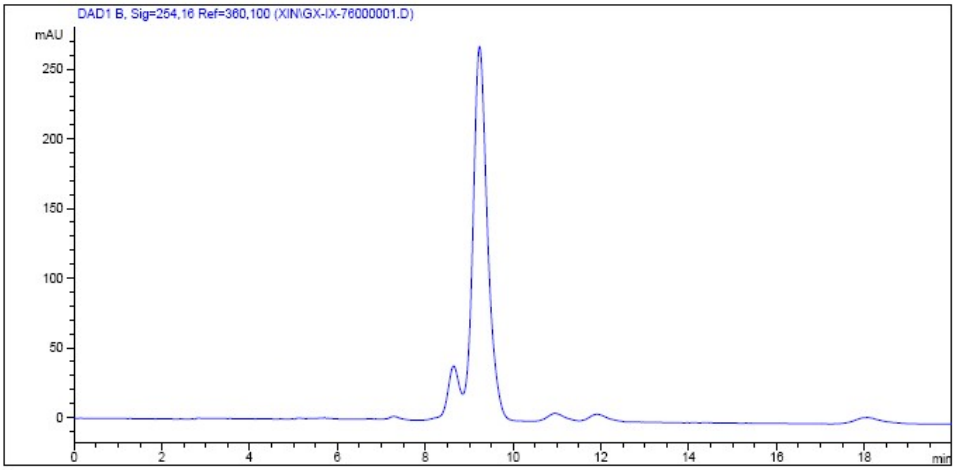


An oven-dried sealed tube under an atmosphere of N_2 was charged with 6-bromopicolinaldehyde **3.9a** (37.2 mg, 0.20 mmol, 100 mol%), (*R*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%), isopropanol (31 μL, 0.4 mmol, 200 mol%), and α-(trifluoromethyl)allyl benzoate (92.1 mg, 0.40 mmol, 200 mol%) were added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 with 0.1% TEA) provided **3.3a** (42.6 mg, 0.144 mmol) as a colorless oil in 72% yield (>20:1 dr).

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 97:3, 1 mL/min, 254 nm), t_{major} = 9.2 min, t_{minor} = 10.9 min; ee = 95%.

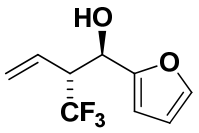


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.153	BB	0.1926	3756.15283	302.96246	49.5806
2	10.731	BB	0.2354	3819.70557	254.11134	50.4194



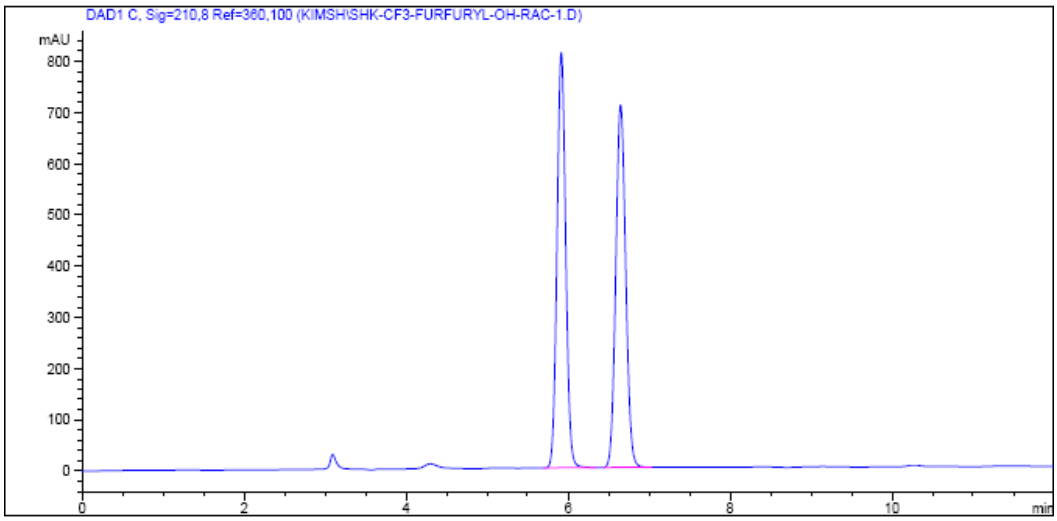
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.233	VB	0.3437	6164.12061	268.64462	97.3834
2	10.952	BV	0.3468	165.62186	5.91306	2.6166

(*1R,2R*)-1-(furan-2-yl)-2-(trifluoromethyl)but-3-en-1-ol 3.3b

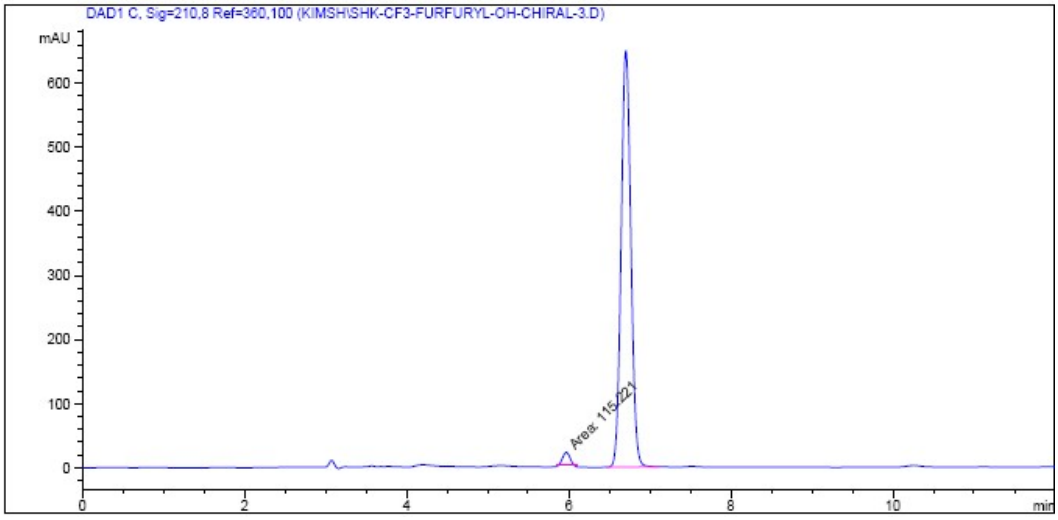


An oven-dried sealed tube under an atmosphere of N_2 was charged with furan-2-carbaldehyde **3.9b** (19.2 mg, 0.20 mmol, 100 mol%), (*R*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), Na_2CO_3 (21.2 mg, 0.20 mmol, 100 mol%). THF (1.0 mL, 0.2 M), H_2O (7.2 μL, 0.4 mmol, 200 mol%), isopropanol (31 μL, 0.4 mmol, 200 mol%), and α-(trifluoromethyl)allyl benzoate (92.1 mg, 0.40 mmol, 200 mol%) were added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 with 0.1% TEA) provided **3.3b** (28.8 mg, 0.139 mmol) as a colorless oil in 69% yield (>20:1 dr).

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), t_{minor} = 6.0 min, t_{major} = 6.7 min; ee = 95%.

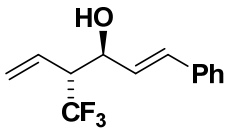


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.913	BB	0.1170	6050.47998	811.74969	50.0694
2	6.646	BB	0.1333	6033.71826	708.57355	49.9306



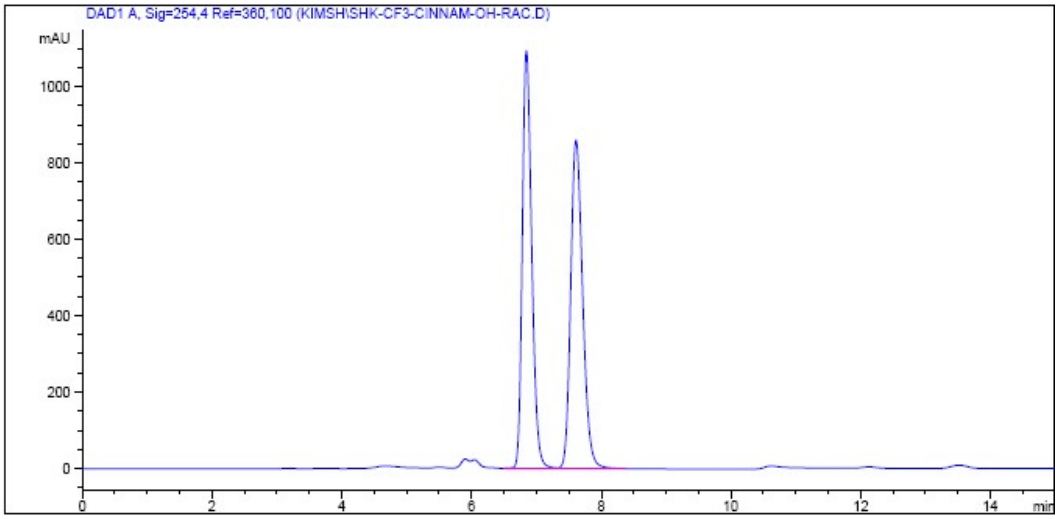
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.967	MM	0.0992	115.22108	19.36737	2.0774
2	6.702	BB	0.1314	5431.05859	650.72015	97.9226

(*3S,4R,E*)-1-phenyl-4-(trifluoromethyl)hexa-1,5-dien-3-ol 3.3c

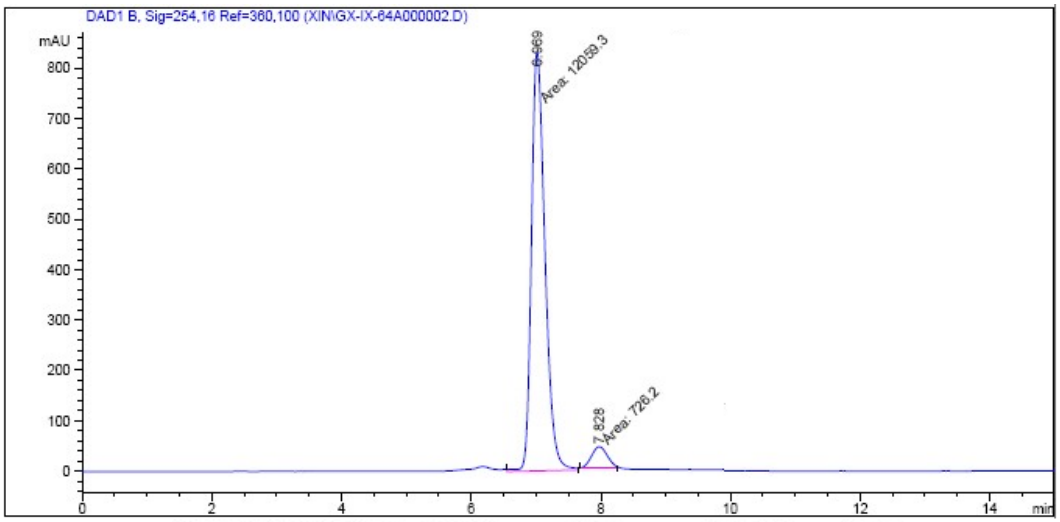


An oven-dried sealed tube under an atmosphere of N_2 was charged with *trans*-cinnamyl alcohol **3.9c** (26.8 mg, 0.20 mmol, 100 mol%), (*R*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), Na_2CO_3 (21.2 mg, 0.20 mmol, 100 mol%). THF (1.0 mL, 0.2 M), H_2O (7.2 μL, 0.4 mmol, 200 mol%), and α-(trifluoromethyl)allyl benzoate (92.1 mg, 0.40 mmol, 200 mol%) were added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 with 0.1% TEA) provided **3.3c** (29.1 mg, 0.120 mmol) as a colorless oil in 60% yield (>20:1 dr).

HPLC: (Chiralcel OB-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 254 nm), t_{major} = 7.0 min, t_{minor} = 7.8 min; ee = 89%.

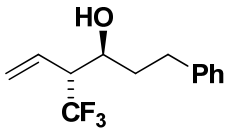


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.844	BV	0.1558	1.10525e4	1094.70068	50.0341
2	7.610	VB	0.1977	1.10375e4	860.45605	49.9659



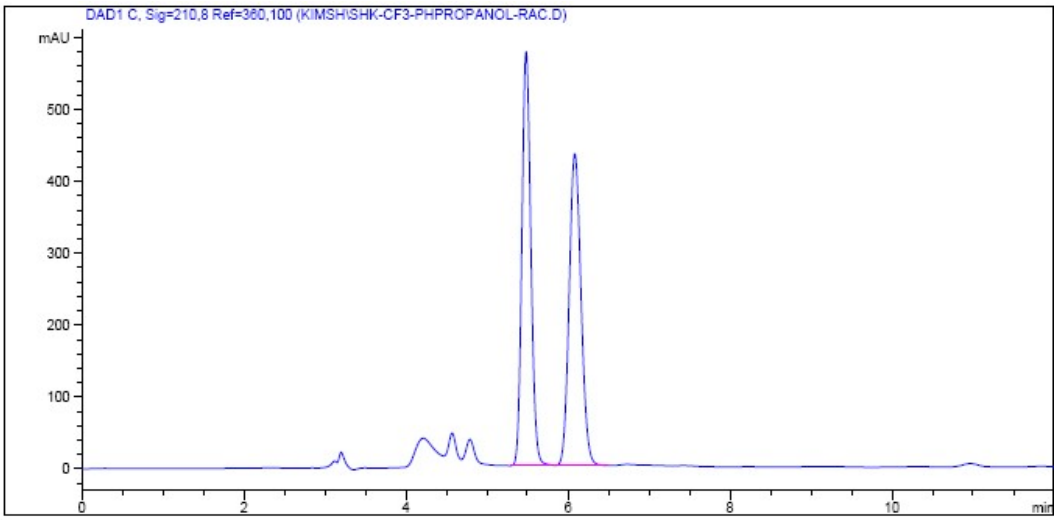
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.969	MM	0.2416	1.20593e4	832.05469	94.3201
2	7.828	MM	0.2849	726.20001	42.47839	5.6799

(*3S,4R*)-1-phenyl-4-(trifluoromethyl)hex-5-en-3-ol 3.3d

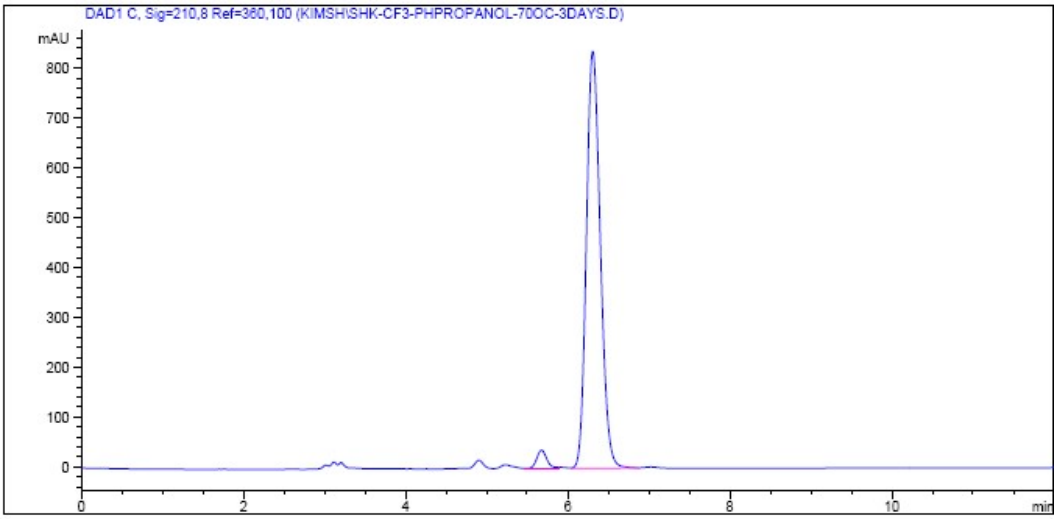


An oven-dried sealed tube under an atmosphere of N_2 was charged with 3-phenylpropanal **3.9d** (26.8 mg, 0.20 mmol, 100 mol%), (*R*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), Na_2CO_3 (21.2 mg, 0.20 mmol, 100 mol%). THF (1.0 mL, 0.2 M), H_2O (7.2 μL, 0.4 mmol, 200 mol%), isopropanol (31 μL, 0.4 mmol, 200 mol%), and α-(trifluoromethyl)allyl benzoate (92.1 mg, 0.40 mmol, 200 mol%) were added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 with 0.1% TEA) provided **3.3d** (31.8 mg, 0.138 mmol) as a colorless oil in 69% yield (>20:1 dr).

HPLC: (Chiralcel OB-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), t_{minor} = 5.8 min, t_{major} = 6.4 min; ee = 94%.

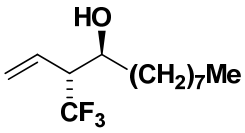


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.481	BV	0.1196	4424.38623	576.07074	50.0408
2	6.082	VB	0.1587	4417.17871	434.20898	49.9592



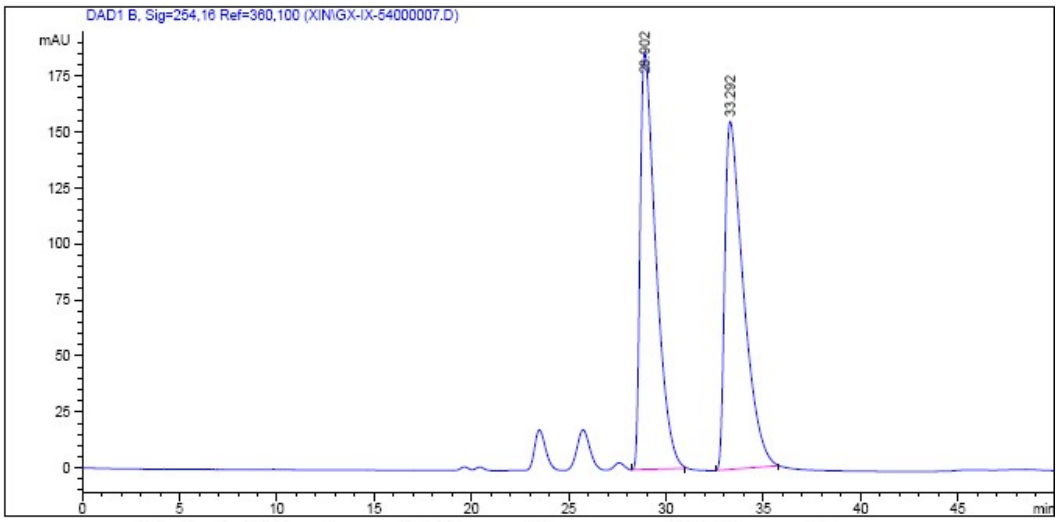
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.674	VB	0.1348	326.82077	37.07567	3.1615
2	6.306	BB	0.1875	1.00108e4	836.92395	96.8385

(*3R,4S*)-3-(trifluoromethyl)dodec-1-en-4-ol 3.3e

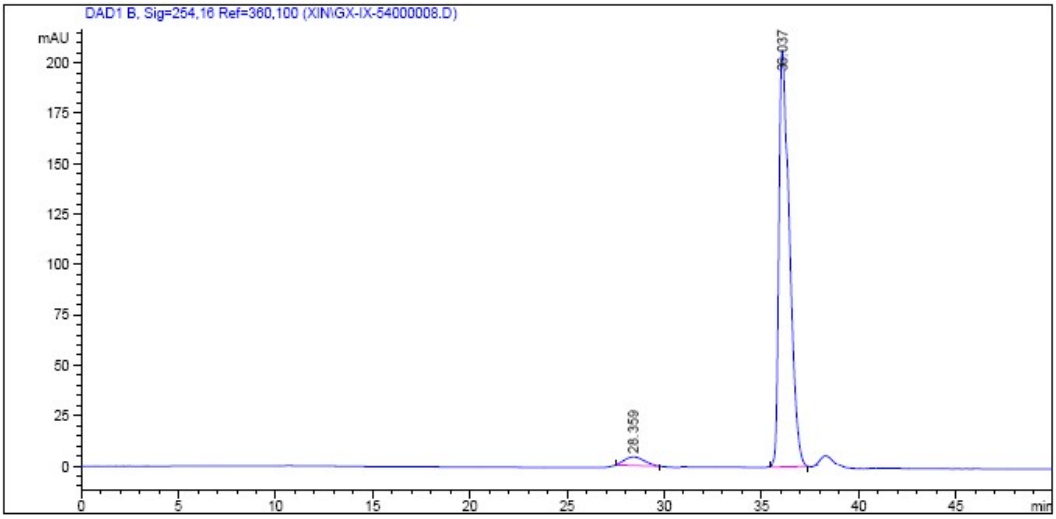


An oven-dried sealed tube under an atmosphere of N_2 was charged with nonanal **3.9e** (28.4 mg, 0.20 mmol, 100 mol%), (*R*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), Na_2CO_3 (21.2 mg, 0.20 mmol, 100 mol%). THF (1.0 mL, 0.2 M), H_2O (7.2 μL, 0.4 mmol, 200 mol%), isopropanol (31 μL, 0.4 mmol, 200 mol%), and α-(trifluoromethyl)allyl benzoate (92.1 mg, 0.40 mmol, 200 mol%) were added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:15 with 0.1% TEA) provided **3.3e** (34.8 mg, 0.138 mmol) as a colorless oil in 69% yield (10:1 dr).

HPLC: Enantiomeric excess was determined by HPLC analysis of the 4-nitrobenzoate derivative of the product (Chiralcel OJ-H column, hexanes:*i*-PrOH = 99:1, 0.75 mL/min, 254 nm), t_{minor} = 28.4 min, t_{major} = 36.1 min; ee = 92%.

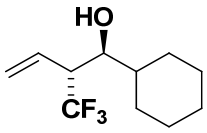


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.902	VB	0.8278	1.04637e4	186.15135	50.2064
2	33.292	BB	0.9714	1.03777e4	155.35107	49.7936



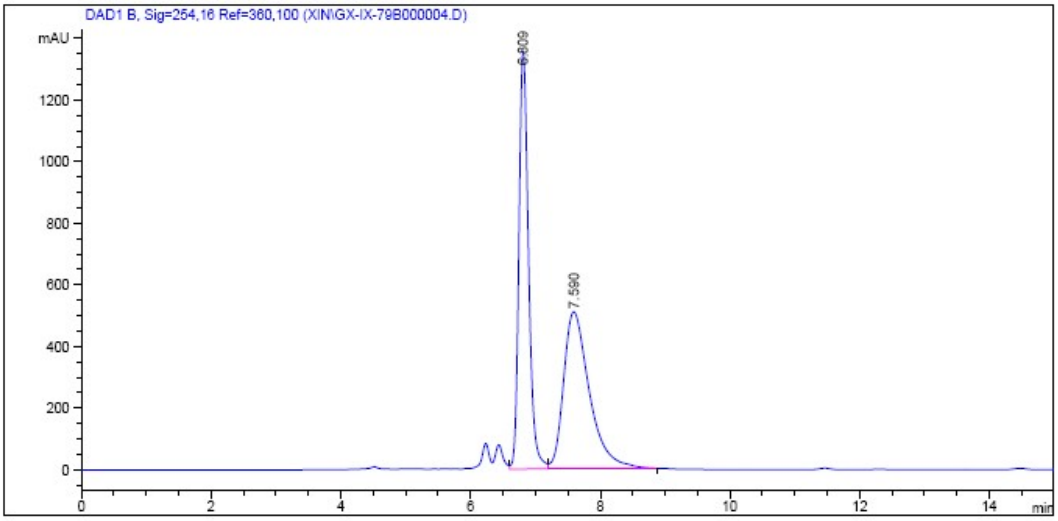
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.359	BB	0.8553	314.13269	4.33558	3.8611
2	36.037	BB	0.5395	7821.75439	206.67958	96.1389

(*1S,2R*)-1-cyclohexyl-2-(trifluoromethyl)but-3-en-1-ol 3.3f

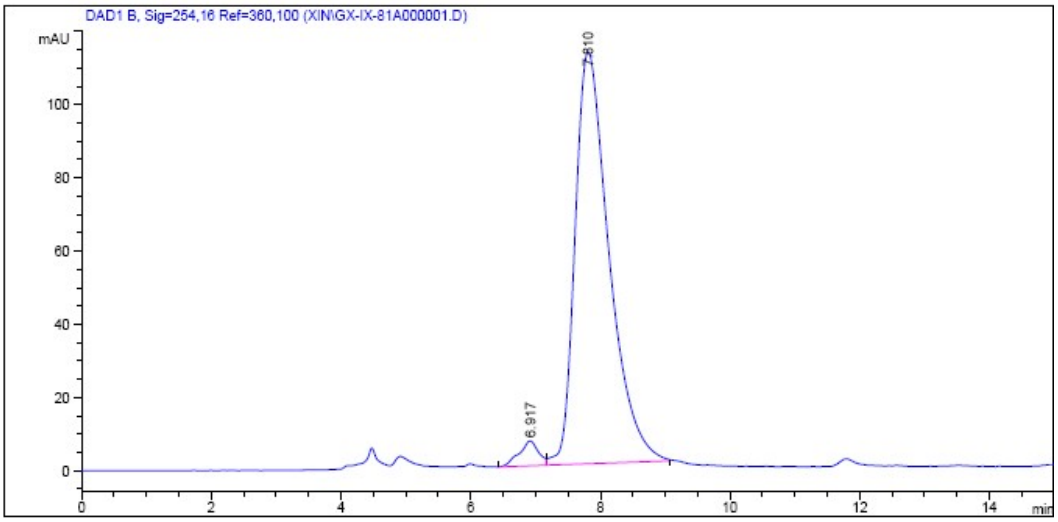


An oven-dried sealed tube under an atmosphere of N_2 was charged with cyclohexanecarbaldehyde **3.9f** (22.4 mg, 0.20 mmol, 100 mol%), (*R*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%), isopropanol (31 μL, 0.4 mmol, 200 mol%), and α-(trifluoromethyl)allyl benzoate (92 mg, 0.40 mmol, 200 mol%) were added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **3.3f** (36.0 mg, 0.162 mmol) as a colorless oil in 81% yield.

HPLC: Enantiomeric excess was determined by HPLC analysis of the 4-nitrobenzoate derivative of the product (Chiralcel OJ-H column, hexanes:*i*-PrOH = 98:2, 0.75 mL/min, 254 nm), t_{minor} = 6.8 min, t_{major} = 7.6 min; ee = 93%.

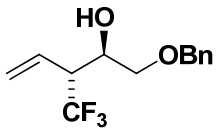


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.809	VV	0.1562	1.40018e4	1358.97339	49.5781
2	7.590	VB	0.4209	1.42401e4	511.36313	50.4219



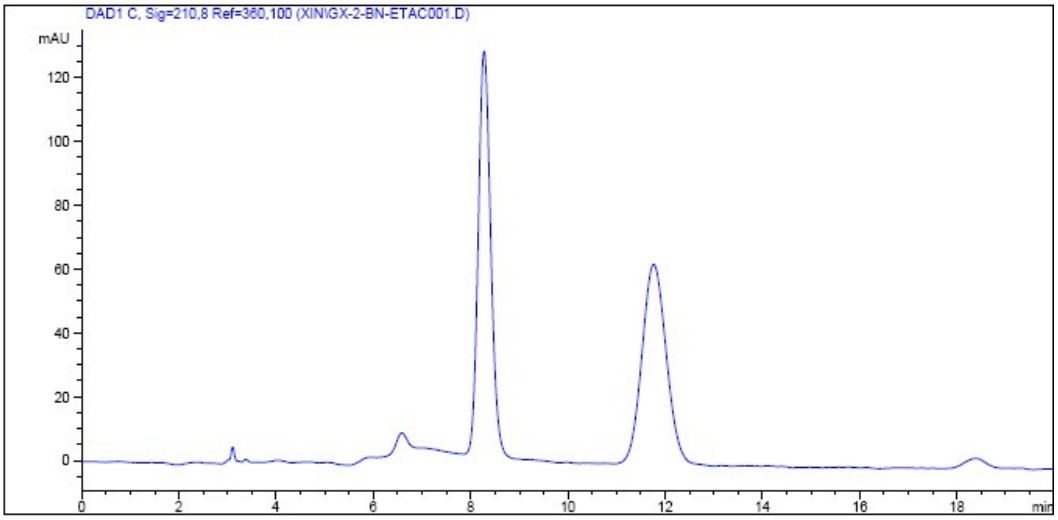
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.917	BV	0.2825	142.20950	6.84231	3.3470
2	7.810	VB	0.5456	4106.68066	112.58008	96.6530

(*2R,3R*)-1-(benzyloxy)-3-(trifluoromethyl)pent-4-en-2-ol 3.3g

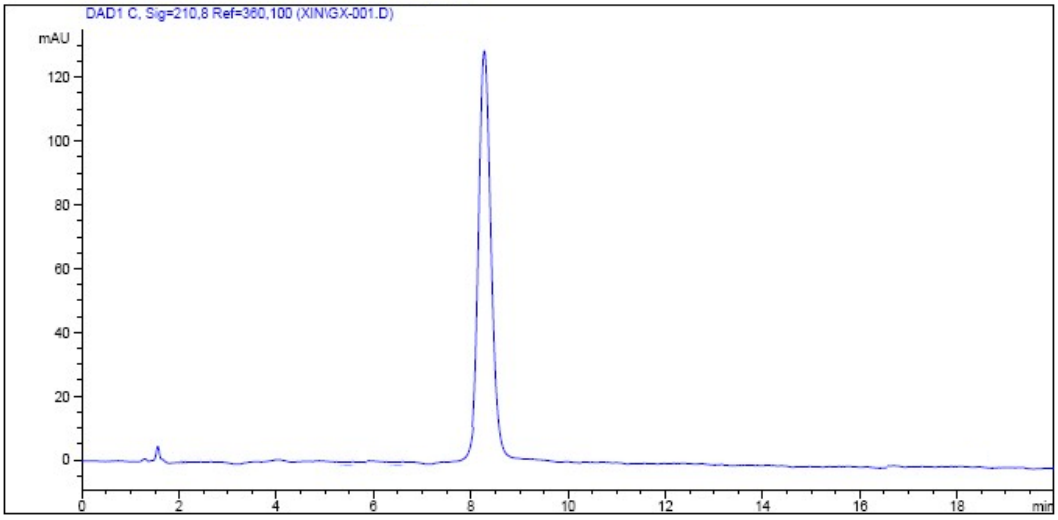


An oven-dried sealed tube under an atmosphere of N_2 was charged with 2-(benzyloxy)acetaldehyde **3.9g** (30.0 mg, 0.20 mmol, 100 mol%), (*R*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), Na_2CO_3 (21.2 mg, 0.20 mmol, 100 mol%). THF (1.0 mL, 0.2 M), H_2O (7.2 μL, 0.4 mmol, 200 mol%), isopropanol (31 μL, 0.4 mmol, 200 mol%), and α-(trifluoromethyl)allyl benzoate (92.1 mg, 0.40 mmol, 200 mol%) were added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 with 0.1% TEA) provided **3.3g** (28.6 mg, 0.110 mmol) as a colorless oil in 55% yield (>20:1 dr).

HPLC: (Chiralcel OB-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 210 nm), t_{major} = 8.3 min, t_{minor} = 11.8 min; ee = 99%.

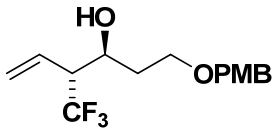


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.273	BB	0.2751	2251.76489	126.82373	50.9004
2	11.761	BB	0.5348	2172.09570	62.59485	49.0996



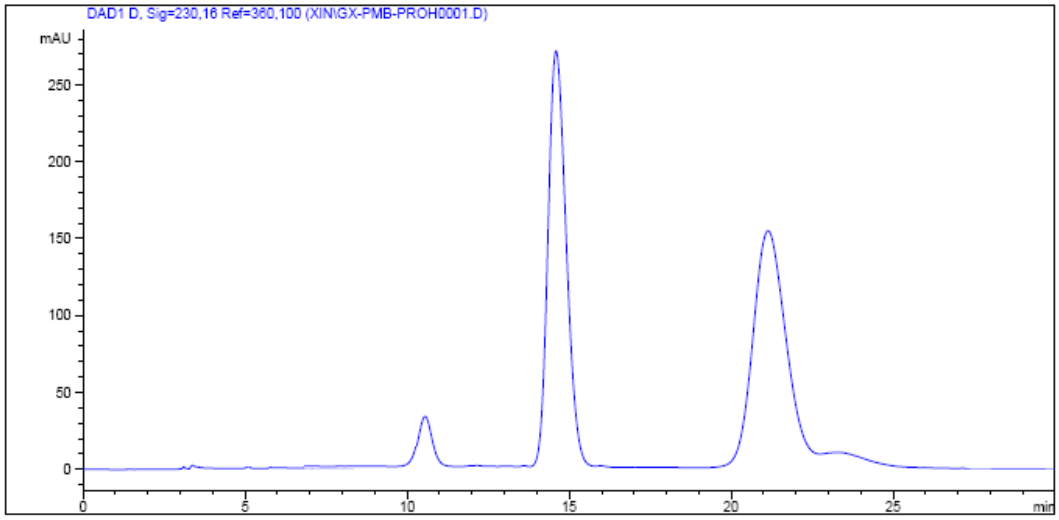
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.185	BB	0.2744	2249.00989	124.94629	100.0000

(*3S,4R*)-1-(4-methoxybenzyloxy)-4-(trifluoromethyl)hex-5-en-3-ol 3.3h

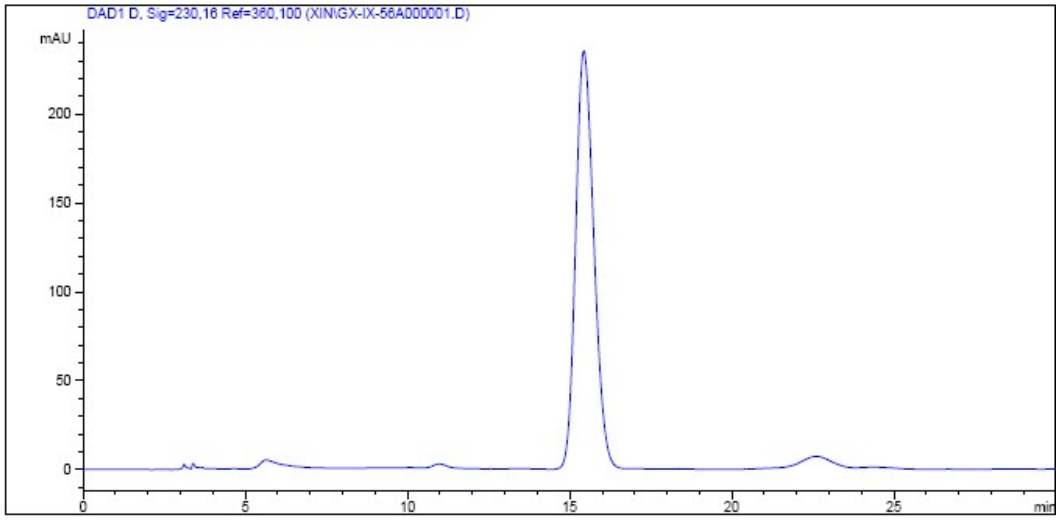


An oven-dried sealed tube under an atmosphere of N_2 was charged with 3-(4-methoxybenzyloxy)propanal **3.9h** (38.8 mg, 0.20 mmol, 100 mol%), (*R*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), Na_2CO_3 (21.2 mg, 0.20 mmol, 100 mol%). THF (1.0 mL, 0.2 M), H_2O (7.2 μL, 0.4 mmol, 200 mol%), isopropanol (31 μL, 0.4 mmol, 200 mol%), and α-(trifluoromethyl)allyl benzoate (92.1 mg, 0.40 mmol, 200 mol%) were added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 with 0.1% TEA) provided **3.3h** (40.8 mg, 0.134 mmol) as a colorless oil in 67% yield (10:1 dr).

HPLC: (Chiralcel OB-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 230 nm), t_{major} = 14.4 min, t_{minor} = 21.1 min; ee = 93%.

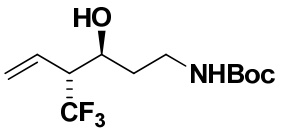


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.588	VB	0.6070	1.05001e4	270.40308	50.8452
2	21.131	BB	1.0598	1.01510e4	149.57124	49.1548



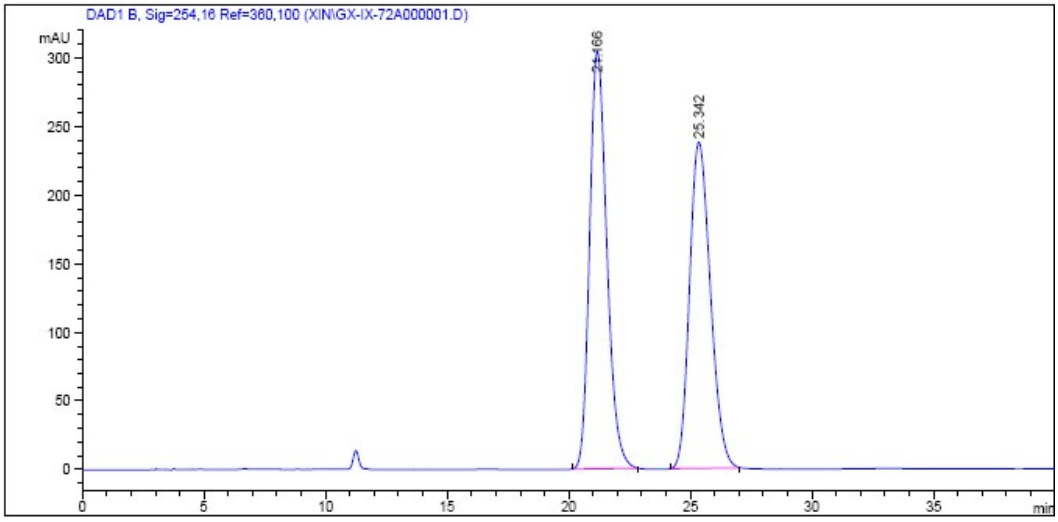
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.433	BB	0.6080	9152.52344	235.20638	96.5063
2	22.591	BB	0.6902	331.33838	5.89070	3.4937

***tert*-butyl (*3S,4R*)-3-hydroxy-4-(trifluoromethyl)hex-5-enylcarbamate 3.3i**

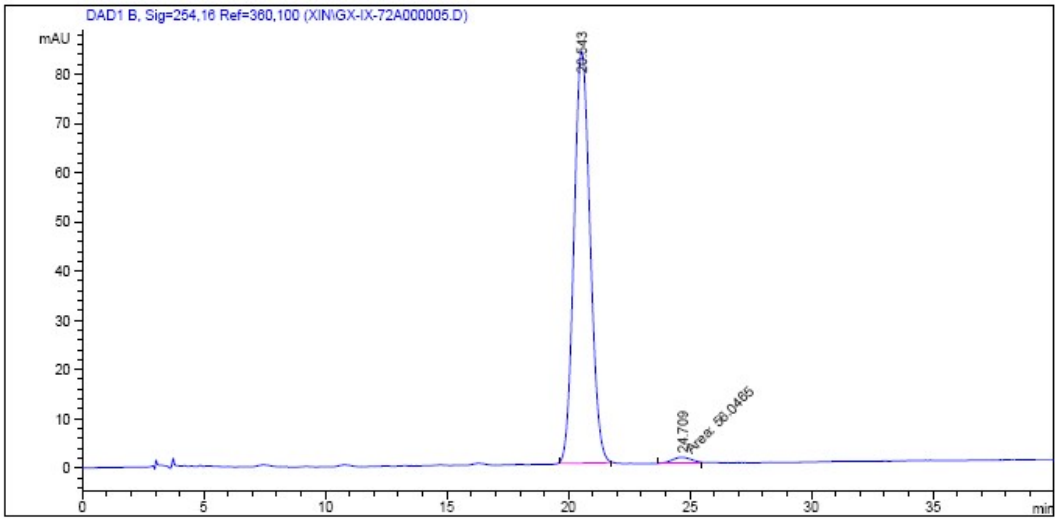


An oven-dried sealed tube under an atmosphere of N_2 was charged with *tert*-butyl 3-oxopropylcarbamate **3.9i** (34.7 mg, 0.2 mmol, 100 mol%), (*R*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (43 mg, 0.2 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 5.0 mmol, 500 mol%), isopropanol (31 μL, 0.4 mmol, 200 mol%), and α-(trifluoromethyl)allyl benzoate (92.1 mg, 0.4 mmol, 200 mol%) were added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 with 0.1% TEA) provided **3.3i** (39.7 mg, 0.140 mmol) as a colorless oil in 70% yield (>20:1 dr).

HPLC: Enantiomeric excess was determined by HPLC analysis of the 4-nitrobenzoate derivative of the product (Chiralcel OJ-H column, hexanes:*i*-PrOH = 98:2, 0.75 mL/min, 254 nm), t_{major} = 20.5 min, t_{minor} = 24.8 min; ee = 97%.

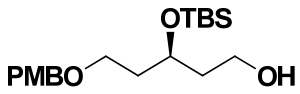


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.166	BB	0.7619	1.49681e4	304.26678	51.3535
2	25.342	BB	0.9301	1.41791e4	237.63631	48.6465



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.543	BB	0.7229	3861.52612	83.59372	98.5694
2	24.709	MM	0.8585	56.04647	1.08809	1.4306

(*S*)-3-(*tert*-butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)pentan-1-ol 3.1j



An oven-dried sealed tube under an atmosphere of N_2 was charged with 3-(4-methoxybenzyloxy)propan-1-ol (750 mg, 3.94 mmol, 100 mol%), (*S*)-**I** (203 mg, 0.197 mmol, 5 mol%), Cs_2CO_3 (128.5 mg, 0.394 mmol, 10 mol%). THF (20.0 mL, 0.2 M) and allyl acetate (858 μL, 7.9 mmol, 200 mol%) were added and the mixture was stirred at 120 ^oC for 22 hr, The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 with 0.1% TEA) provided (*S*)-1-(4-methoxybenzyloxy)hex-5-en-3-ol (763.5 mg, 3.23 mmol) as a colorless oil in 82% yield, 96% ee.

Followed by the TBS-protection/Ozonolysis sequence reported by the same group,[15] the title compund **3.1j** was obtained (989 mg, 2.79 mmol) as a colorless oil in 86% yield over two steps.

TLC (SiO_2): R_f = 0.3 (ethyl acetate:hexanes, 1:2).

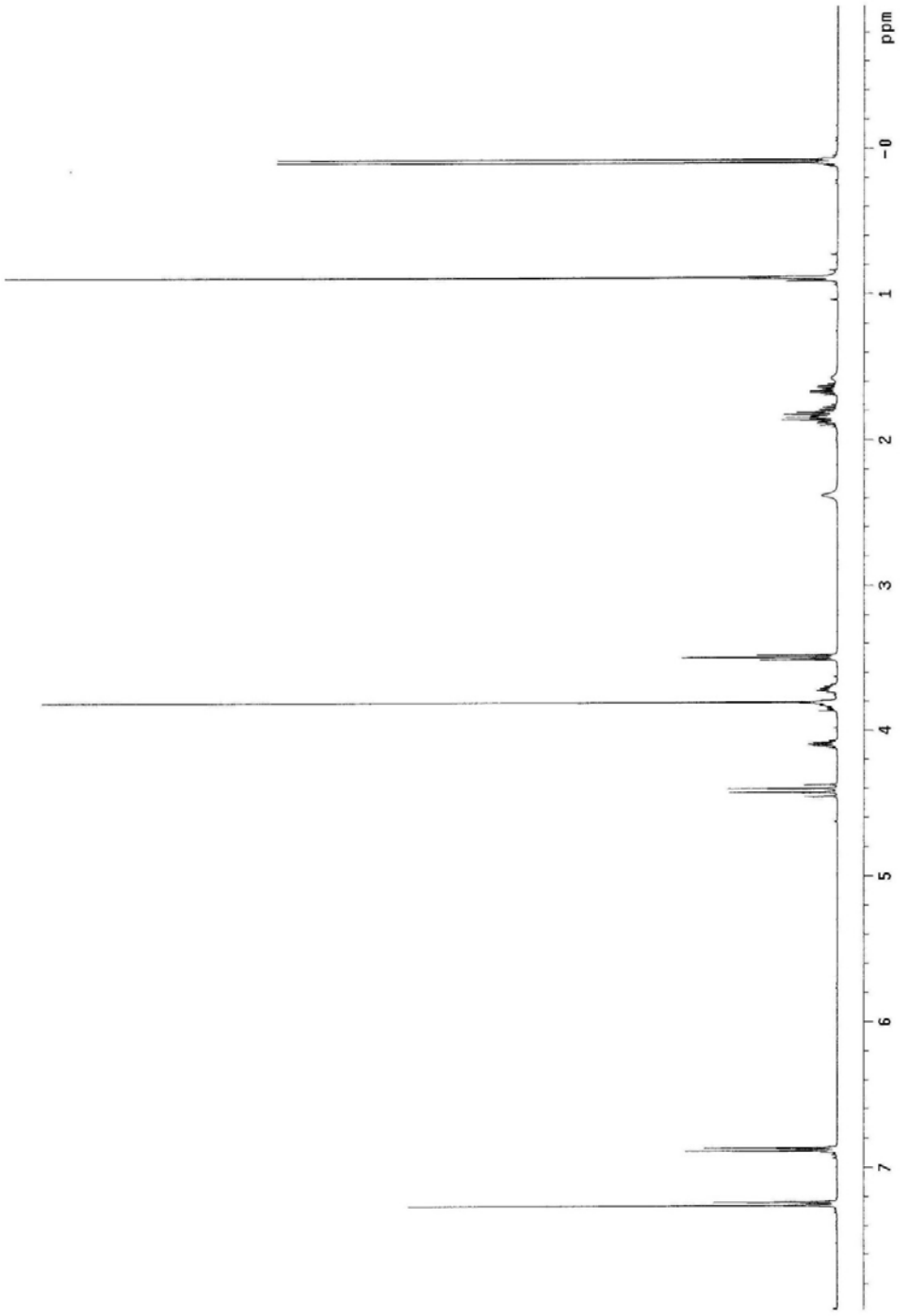
^{1}H NMR (400 MHz, $CDCl_3$): δ7.26-7.24 (m, 2H), 6.89-6.87 (m, 2H), 4.45-4.37 (m, 2H), 4.12-4.07 (m, 1H), 3.87-3.80 (m, 1H), 3.81 (s, 3H), 3.75-3.68 (m, 1H), 3.49 (t, *J* = 6.4 Hz, 2H), 2.38 (br, 1H), 1.91-1.76 (m, 3H), 1.69-1.61 (m, 1H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 130.5, 129.3, 113.8, 72.7, 69.1, 66.5, 60.1, 55.3, 38.2, 36.7, 25.8, 17.9, -4.7.

$[\alpha]_D^{25}$ = -5.38 (c =1.3, CH_2Cl_2).

FTIR (neat): 3413, 2928, 2856, 1586, 1513, 1464, 1360, 1247, 1089, 1035, 838, 774, 1028, 988, 906, 835, 786, 763, 718, 698 cm^{-1}.

HRMS (CI) Calcd. for $C_{19}H_{34}O_4NaSi$ $[M+Na]^+$: 377.2119, Found: 377.2119.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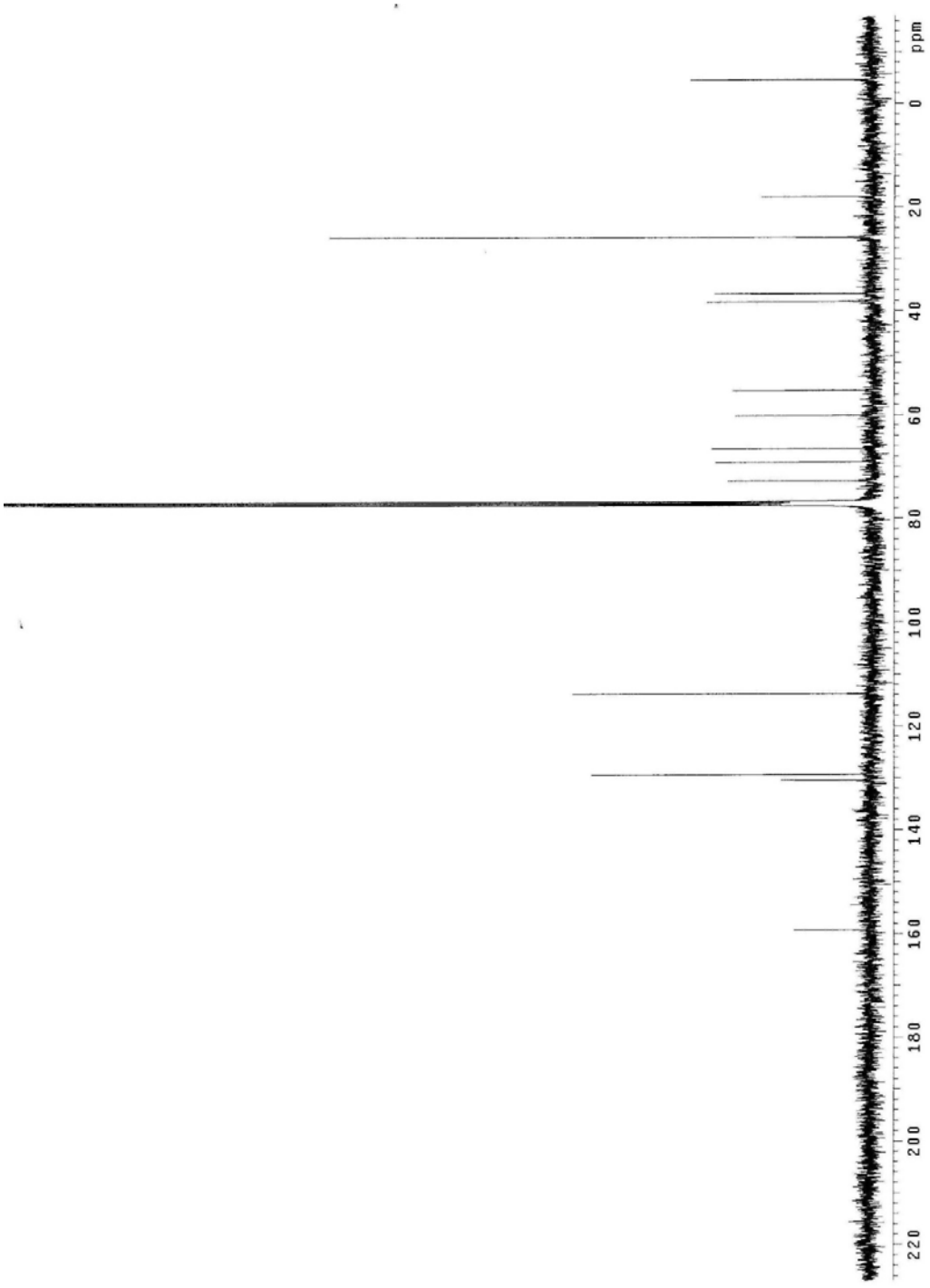
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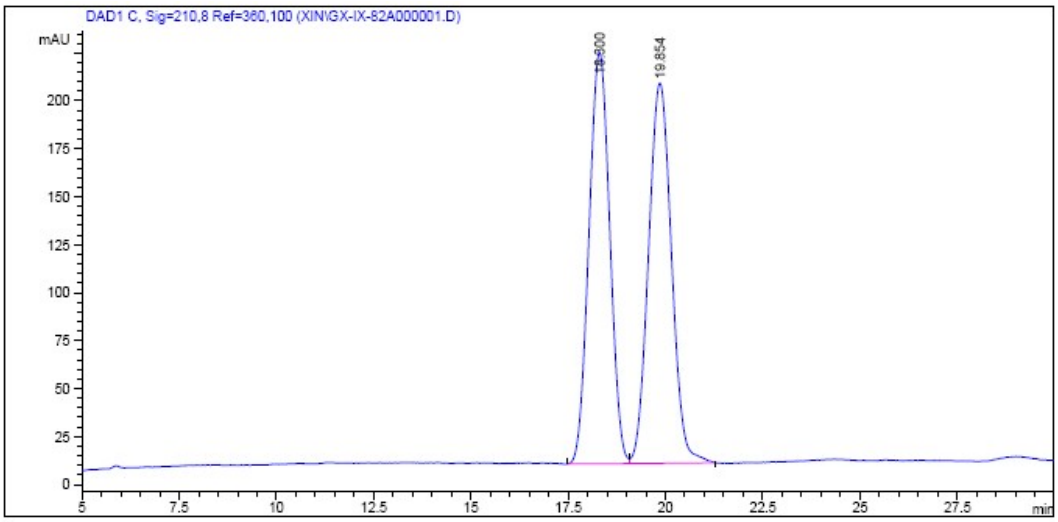
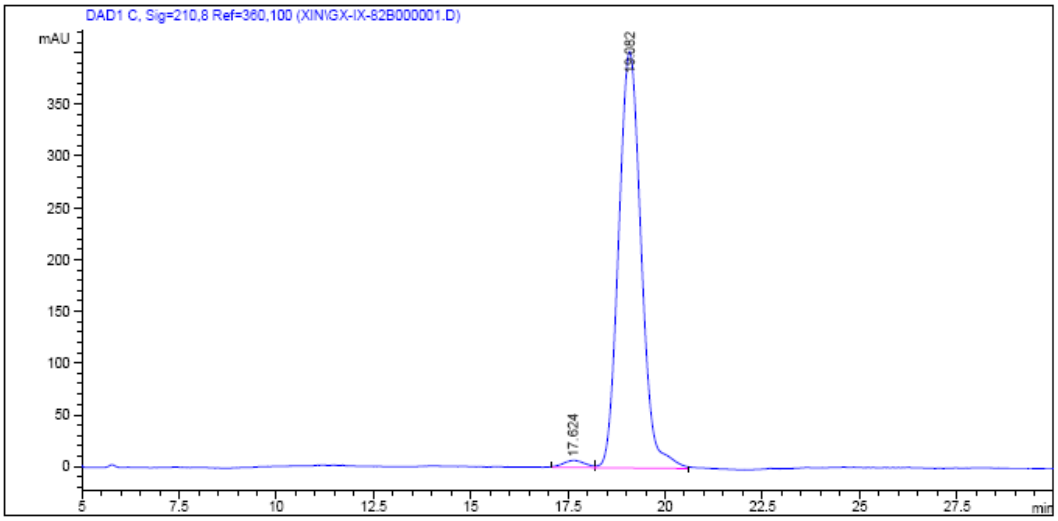
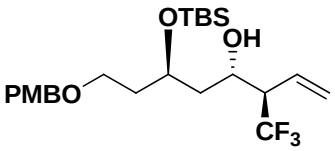


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.300	BV	0.5773	7964.76172	214.46021	49.4415
2	19.854	VB	0.6052	8144.69092	198.29793	50.5585



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.624	BV	0.4694	266.60895	6.79990	1.6194
2	19.082	VB	0.6256	1.61967e4	402.39157	98.3806

(*3R,4S,6R*)-6-(*tert*-butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)-3-(trifluoromethyl)oct-1-en-4-ol 3.3j



An oven-dried sealed tube under an atmosphere of N_2 was charged with (*S*)-3-(*tert*-butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)pentan-1-ol **3.1j** (70.9 mg, 0.20 mmol, 100 mol%), (*R*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), Na_2CO_3 (21.2 mg, 0.20 mmol, 100 mol%). THF (1.0 mL, 0.2 M), H_2O (7.2 μL, 0.4 mmol, 200 mol%), and α-(trifluoromethyl)allyl benzoate (92.1 mg, 0.40 mmol, 200 mol%) were added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 with 0.1% TEA) provided **3.3j** (66.6 mg, 0.144 mmol) as a colorless oil in 72% yield (>20:1 dr).

TLC (SiO_2): R_f = 0.4 (ethyl acetate: hexanes, 1:5).

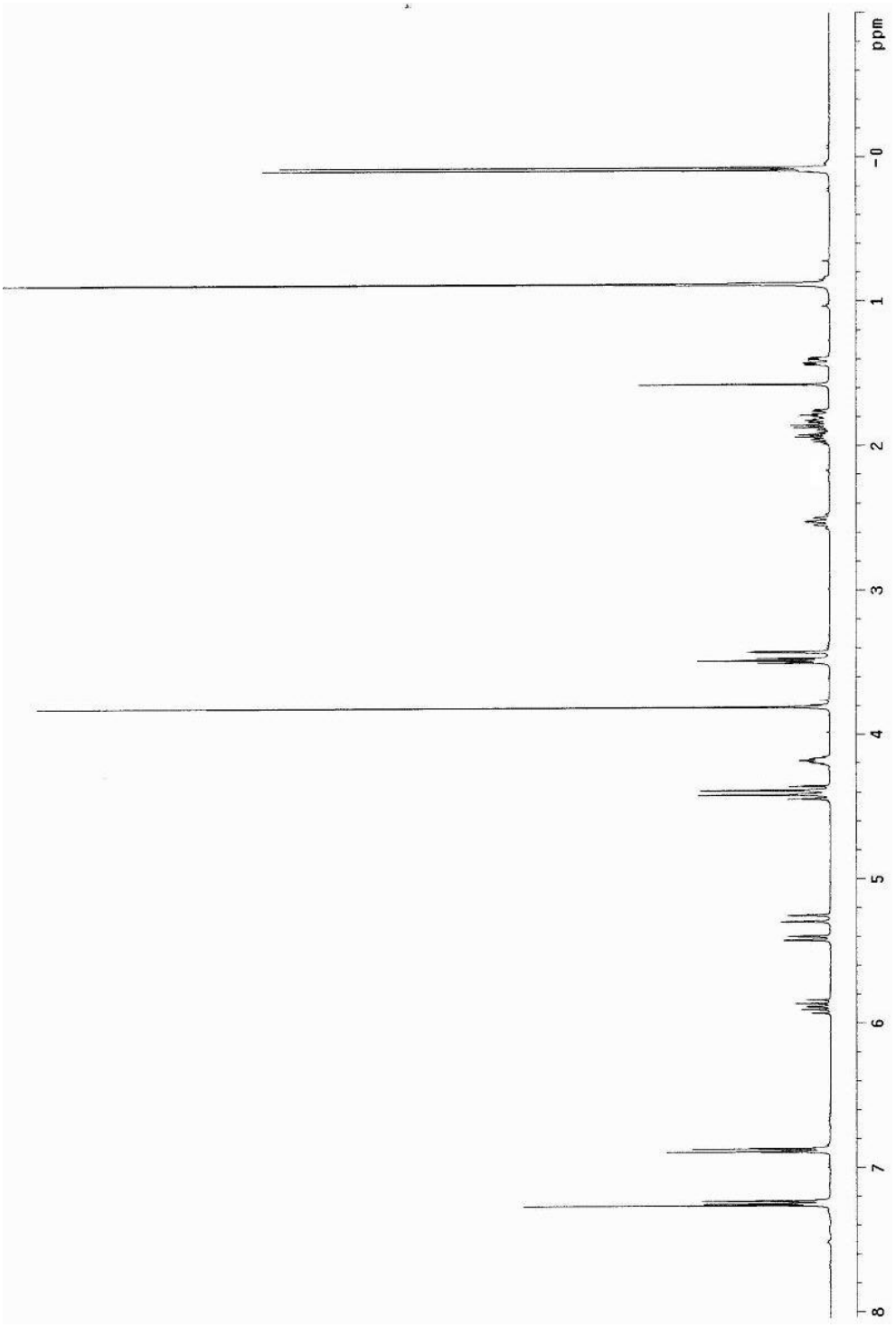
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.23 (m, 2H), 6.89-6.87 (m, 2H), 5.88 (dt, *J* = 17.2, 9.6 Hz, 1H), 5.41 (d, *J* = 9.6 Hz, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 4.45-4.36 (m, 3H), 4.21-4.15 (m, 1H), 3.81 (s, 3H), 3.49 (t, *J* = 6.0 Hz, 2H), 3.42 (d, *J* = 2.4 Hz, 1H), 2.52 (pd, *J* = 9.6, 2.0 Hz, 1H), 1.99-1.75 (m, 3H), 1.41 (ddd, *J* = 14.4, 4.8, 2.4 Hz, 1H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 130.3, 129.3, 128.0, 126.2 (q, *J* = 279.7 Hz), 122.9, 113.8, 72.7, 68.6, 66.2, 65.7, 55.3, 54.1 (q, *J* = 24.5 Hz), 39.6, 36.0, 25.7, 17.9, -4.8, -4.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ -67.66 (d, *J* = 10.0 Hz).

FTIR (neat): 3455, 2953, 2930, 2857, 1613, 1514, 1464, 1302, 1250, 1172, 1094, 1037, 932, 836, 776 cm^{-1}.

HRMS (CI) Calcd. for $C_{23}H_{38}O_4F_3Si$ $[M+H]^+$: 463.2486, Found: 463.2486.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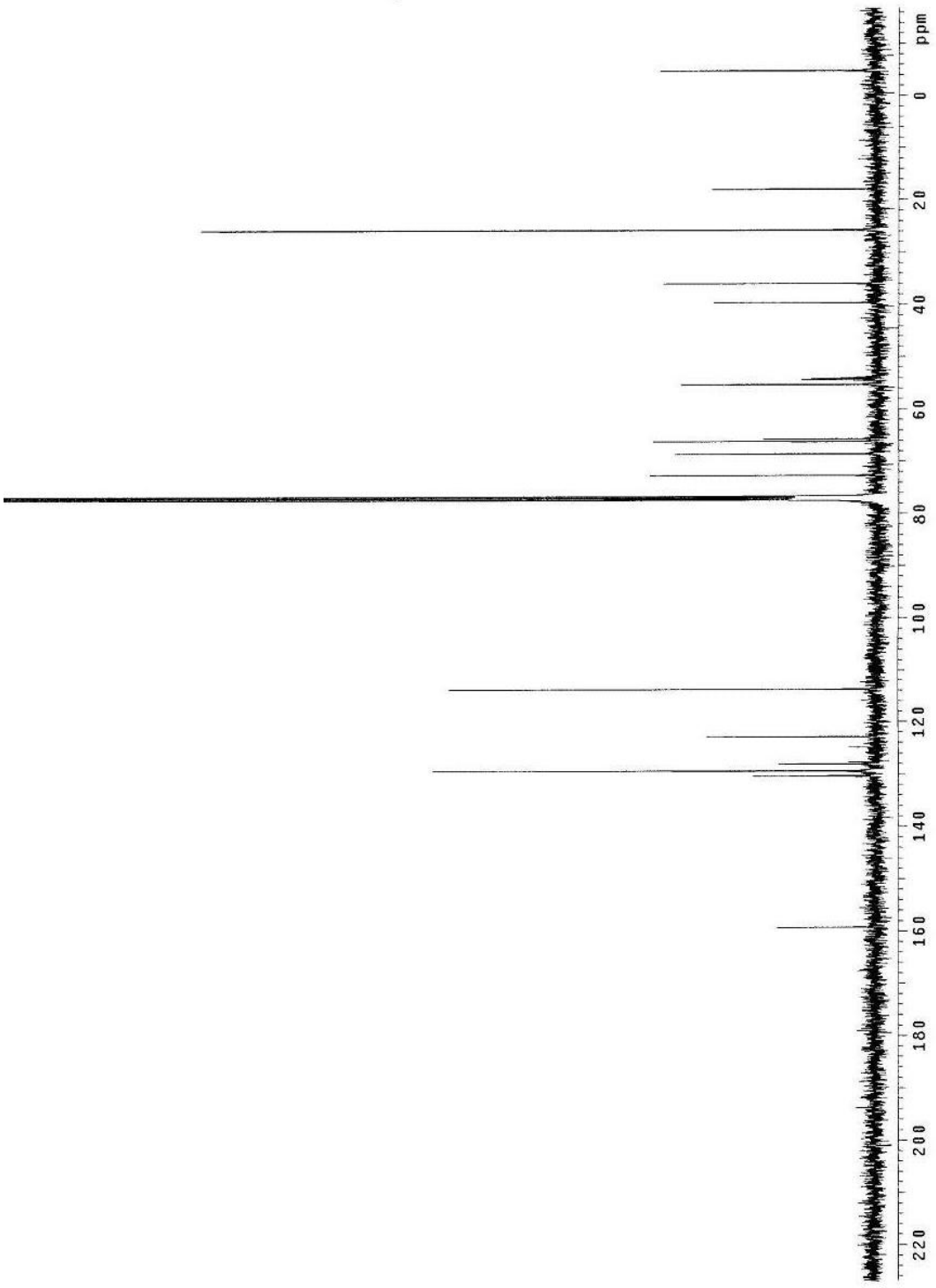
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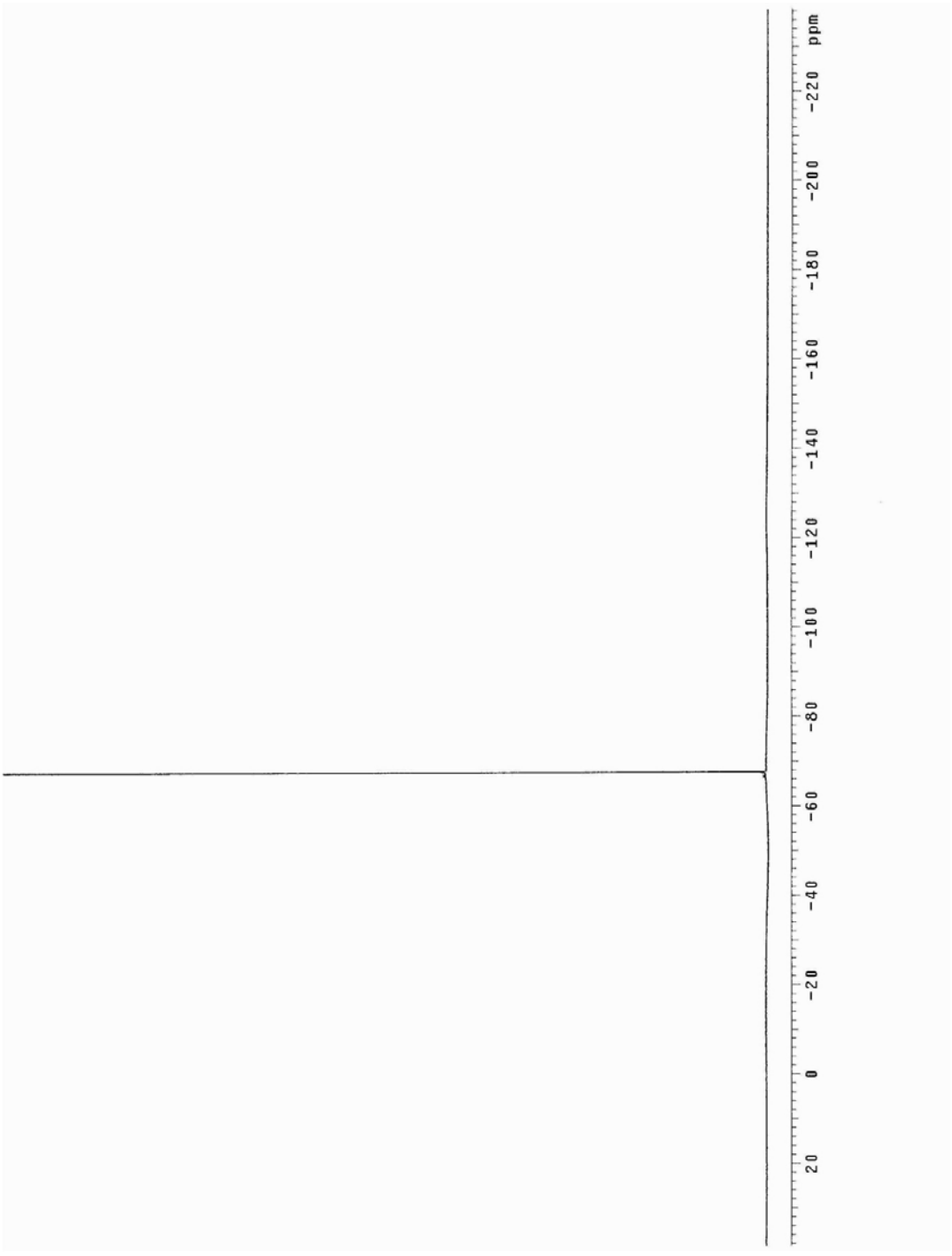
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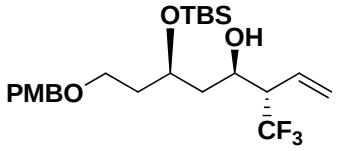
ppm

(*3S,4R,6R*)-6-(*tert*-butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)-3-(trifluoromethyl)oct-1-en-4-ol *iso*-3.3j



An oven-dried sealed tube under an atmosphere of N_2 was charged with (*S*)-3-(*tert*-butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)pentan-1-ol **3.1j** (70.9 mg, 0.20 mmol, 100 mol%), (*S*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), Na_2CO_3 (21.2 mg, 0.20 mmol, 100 mol%). THF (1.0 mL, 0.2 M), H_2O (7.2 μL, 0.4 mmol, 200 mol%), and α-(trifluoromethyl)allyl benzoate (92.1 mg, 0.40 mmol, 200 mol%) were added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 with 0.1% TEA) provided ***iso*-3.3j** (73.1 mg, 0.158 mmol) as a colorless oil in 79% yield (>20:1 dr).

TLC (SiO_2): R_f = 0.4 (ethyl acetate: hexanes, 1:5).

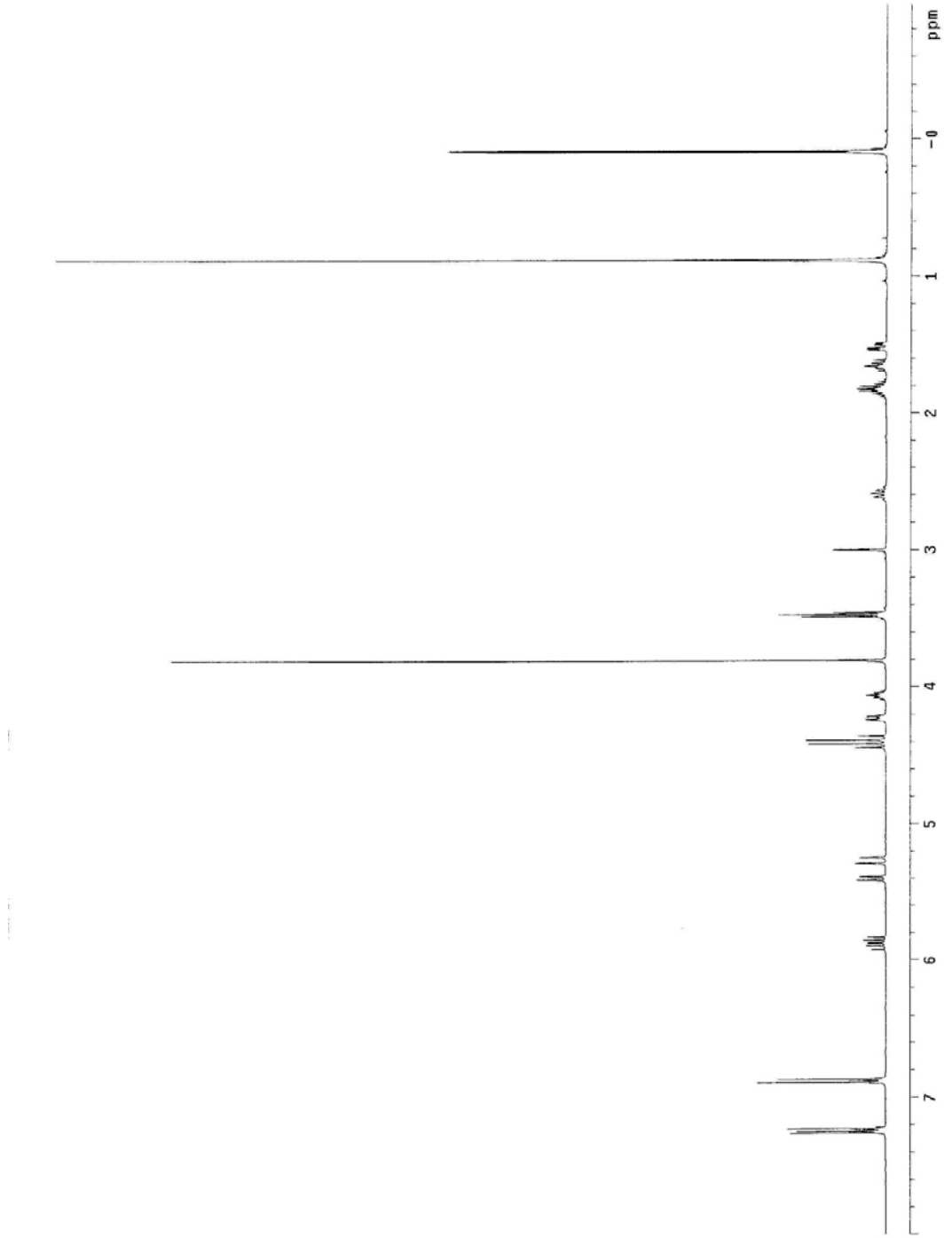
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.22 (m, 2H), 6.90-6.86 (m, 2H), 5.87 (dtd, *J* = 17.2, 9.6, 0.8 Hz, 1H), 5.40 (dd, *J* = 9.6, 0.8 Hz, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 4.44-4.36 (m, 2H), 4.23 (dq, *J* = 9.6, 2.8 Hz 1H), 4.09-4.03 (m, 1H), 3.80 (s, 3H), 3.47 (t, *J* = 6.08 Hz, 2H), 3.00 (d, *J* = 2.4 Hz, 1H), 2.59 (pd, *J* = 9.6, 2.4 Hz, 1H), 1.89-1.75 (m, 2H), 1.69-1.61 (m, 1H), 1.51 (ddd, *J* = 14.4, 4.8, 2.8 Hz, 1H), 0.88 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 130.2, 129.3, 127.9, 126.2 (q, *J* = 279.0 Hz), 122.8, 113.7, 72.7, 69.8, 67.2, 66.1, 55.2, 54.1 (q, *J* = 24.6 Hz), 41.1, 37.5, 25.8, 17.9, -4.3, -4.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ -67.65 (d, *J* = 10.0 Hz).

FTIR (neat): 3454, 2954, 2920, 2850, 1623, 1534, 1474, 1291, 1250, 1172, 1094, 1037, 932, 836, 780 cm^{-1}.

HRMS (CI) Calcd. for $C_{23}H_{38}O_4F_3Si$ $[M+H]^+$: 463.2486, Found: 463.2486.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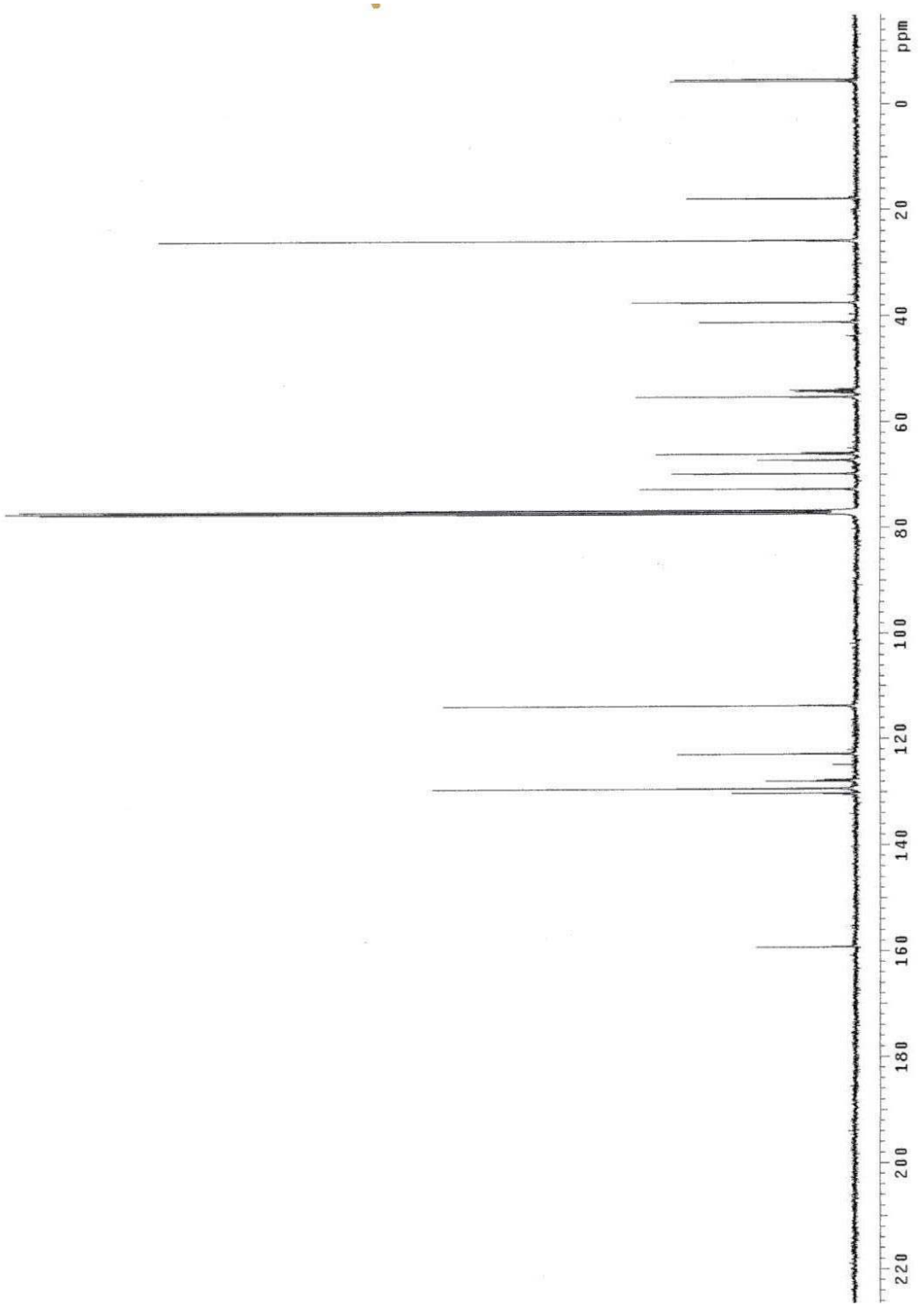
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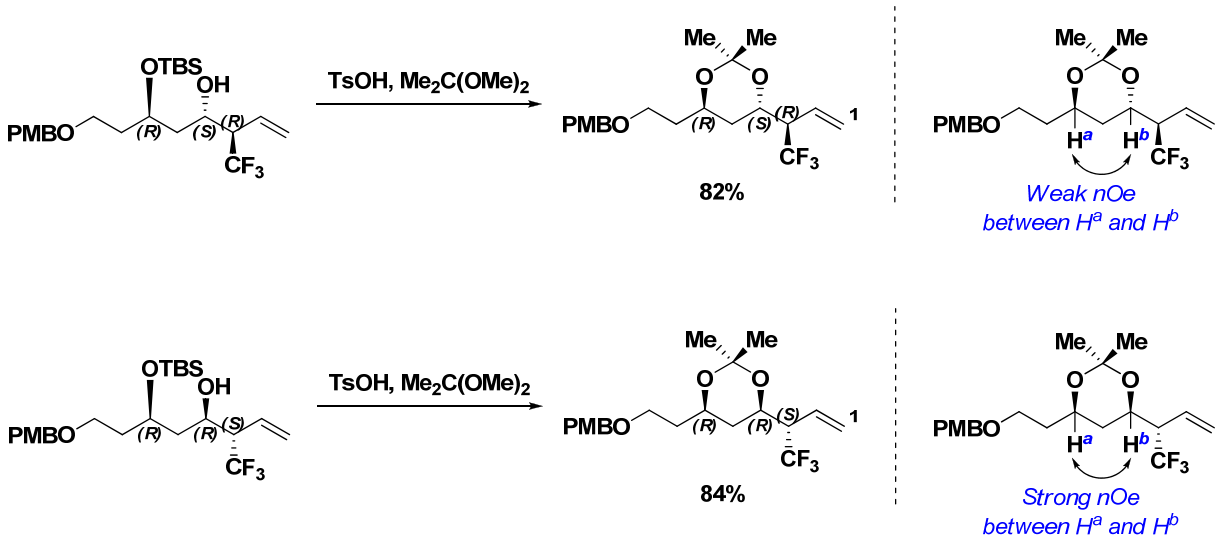
ppm

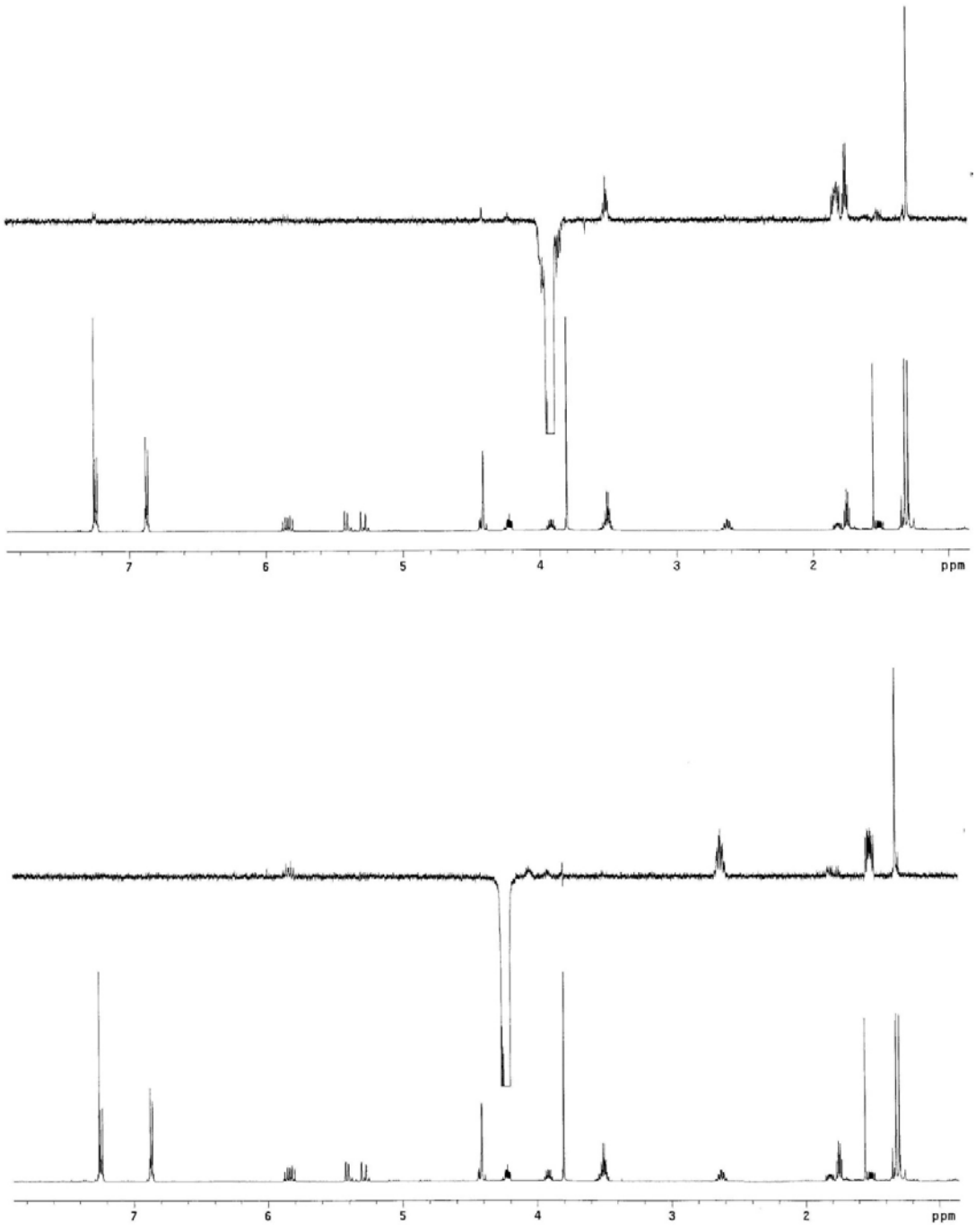
NOE experiments were performed for acetonides derived from **3.3j** and ***iso*-3.3j** using pure samples.



Because the configuration of the β-chiral center derived from *(S)*-**I** was known based on previous work,[16] also the *anti* relationship of the two newly formed chiral centers has been determined by comparison with reported racemic compounds, the absolute stereochemistry outcome could be identified by studying the relative stereochemistry of the newly formed chiral centers with the existed β-chiral center.

Desilylation of **3j** which comes from the reaction using *(R)*-**I** as catalyst and ***iso*-3j** which comes from the reaction using *(S)*-**I** as catalyst, followed by acetonide formation in one-pot, provided the *anti*- and *syn*-cyclic acetal as single diastereomer, repectively. This observation suggested the configuration of the two newly formed chiral centers in **3j** was (3*R*, 4*S*), and (3*S*, 4*R*) in ***iso*-3j**. Hence the absolute stereochemistry outcome has been identified.

(Note: The absence of nOe between H^a and H^b in acetonide derivitive of **3j** suggests a 1,3 trans configuration of the two side chains on the cyclic acetal; and the observation of nOe between H^a and H^b in acetonide derivitive of ***iso*-3j** suggest a 1,3 cis configuration of the two side chains on the cyclic acetal.)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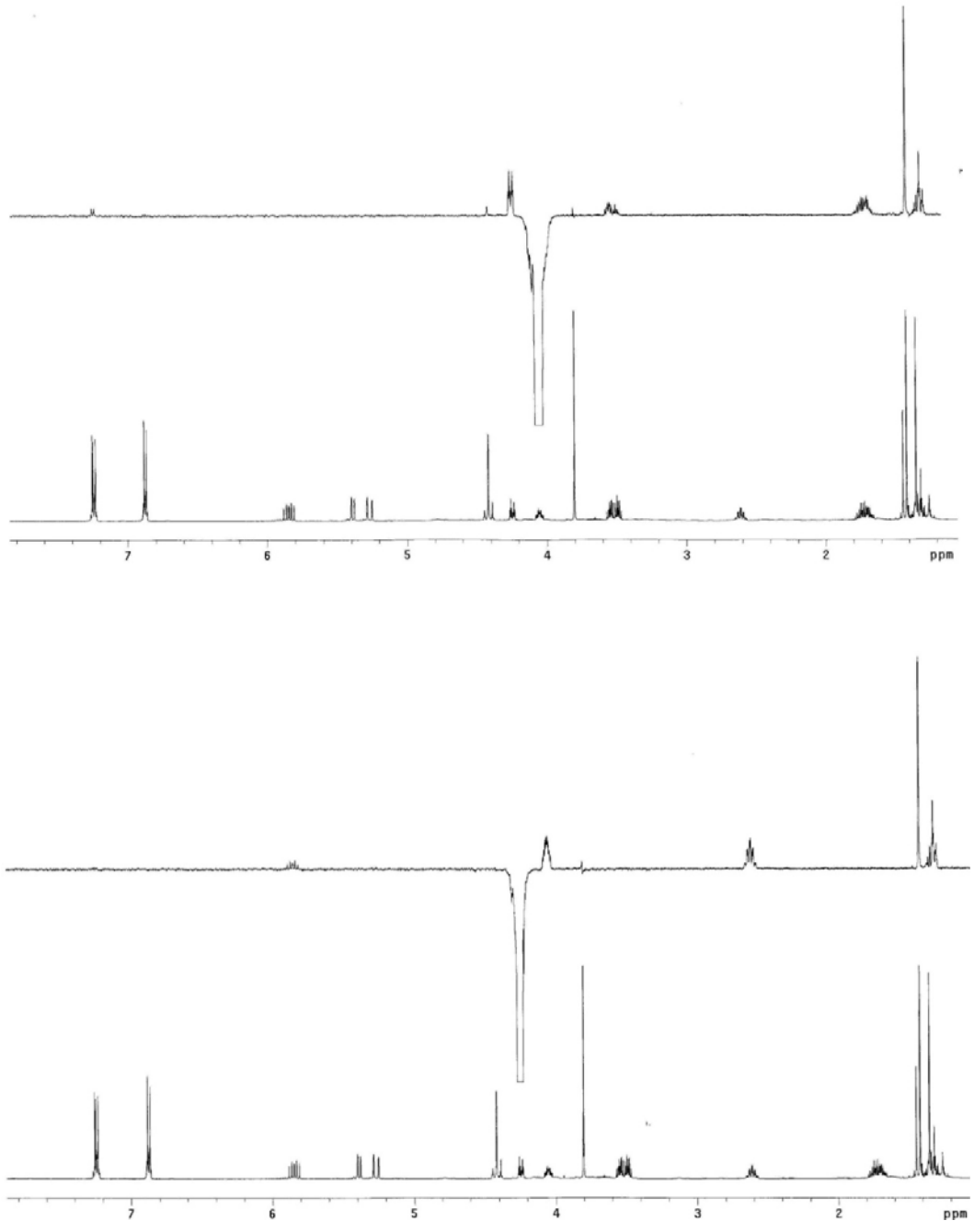
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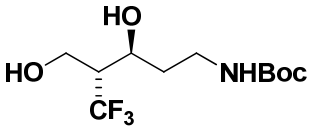
***tert*-butyl (*3S,4R*)-5,5,5-trifluoro-3-hydroxy-4-(hydroxymethyl)pentylcarbamate 3.4i**



An oven-dried round bottom flask under atmosphere of N_2 was charged with *tert*-butyl (*3S,4R*)-3-hydroxy-4-(trifluoromethyl)hex-5-enylcarbamate **3.3i** (206.8 mg, 0.730 mmol, 100 mol%). DCM (14.6 mL, 0.05 M) was added and the mixture was stirred at -78 ^oC with ozone bubbled through until TLC showed full consumption of **3i**. A solution of $NaBH_4$ (276.2 mg, 7.3 mmol, 1000 mol%) in ethanol (50 mL, 0.95) and water (5 mL) was added dropwise and the reaction mixture was stirred at 0 ^oC for one hour and slowly warmed up to ambient temperature and stirred overnight. The reaction mixture was concentrated *in vacuo*, and the product was extracted with ethyl acetate (30 mL/3 times). After removing the solvent, purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:1 with 0.1% TEA) provided **3.4i** (197.1 mg, 0.686 mmol) as a colorless oil in 94% yield as a single diastereomer.[17]

TLC (SiO_2): R_f = 0.15 (ethyl acetate:hexanes, 1:1).

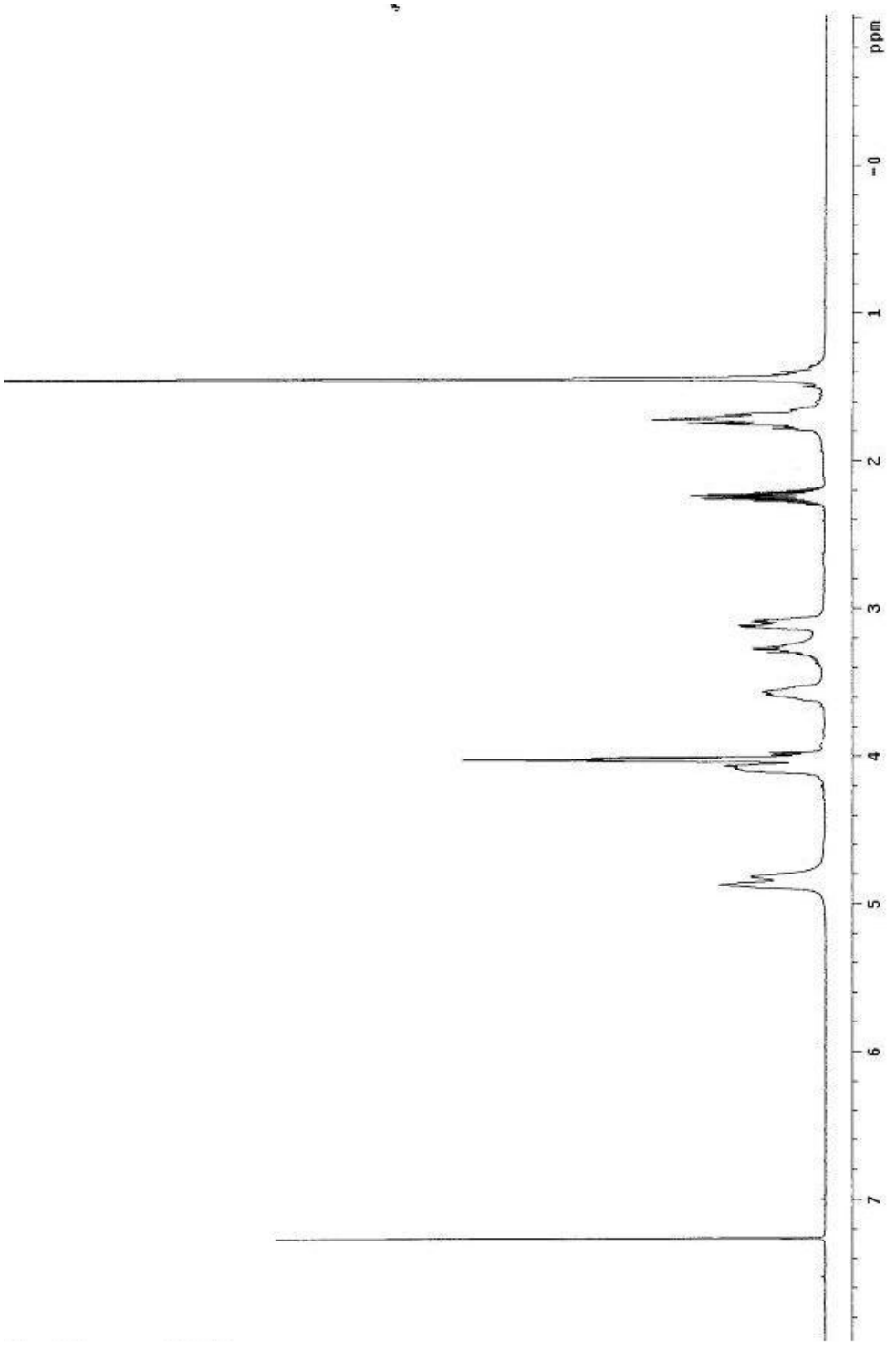
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.87 (br, 1H), 4.81 (br, 1H), 4.11-3.87 (m, 3H), 3.58-3.53 (m, 1H), 3.31-3.24 (m, 1H), 3.12-3.08 (m, 1H), 2.28-2.20 (m, 1H), 1.79-1.65 (m, 1H), 1.44 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 126.6 (q, J = 279.0 Hz), 80.4, 66.2, 59.0, 49.6 (q, J = 23.8 Hz), 37.4, 36.5, 28.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ -66.87 (d, J = 10.0 Hz).

FTIR (neat): 3350, 2979, 1685, 1522, 1368, 1253, 1166, 1129, 866 cm^{-1}.

HRMS (CI) Calcd. for $C_{11}H_{21}NO_4F_3$ $[M+H]^+$: 288.1423, Found: 288.1421.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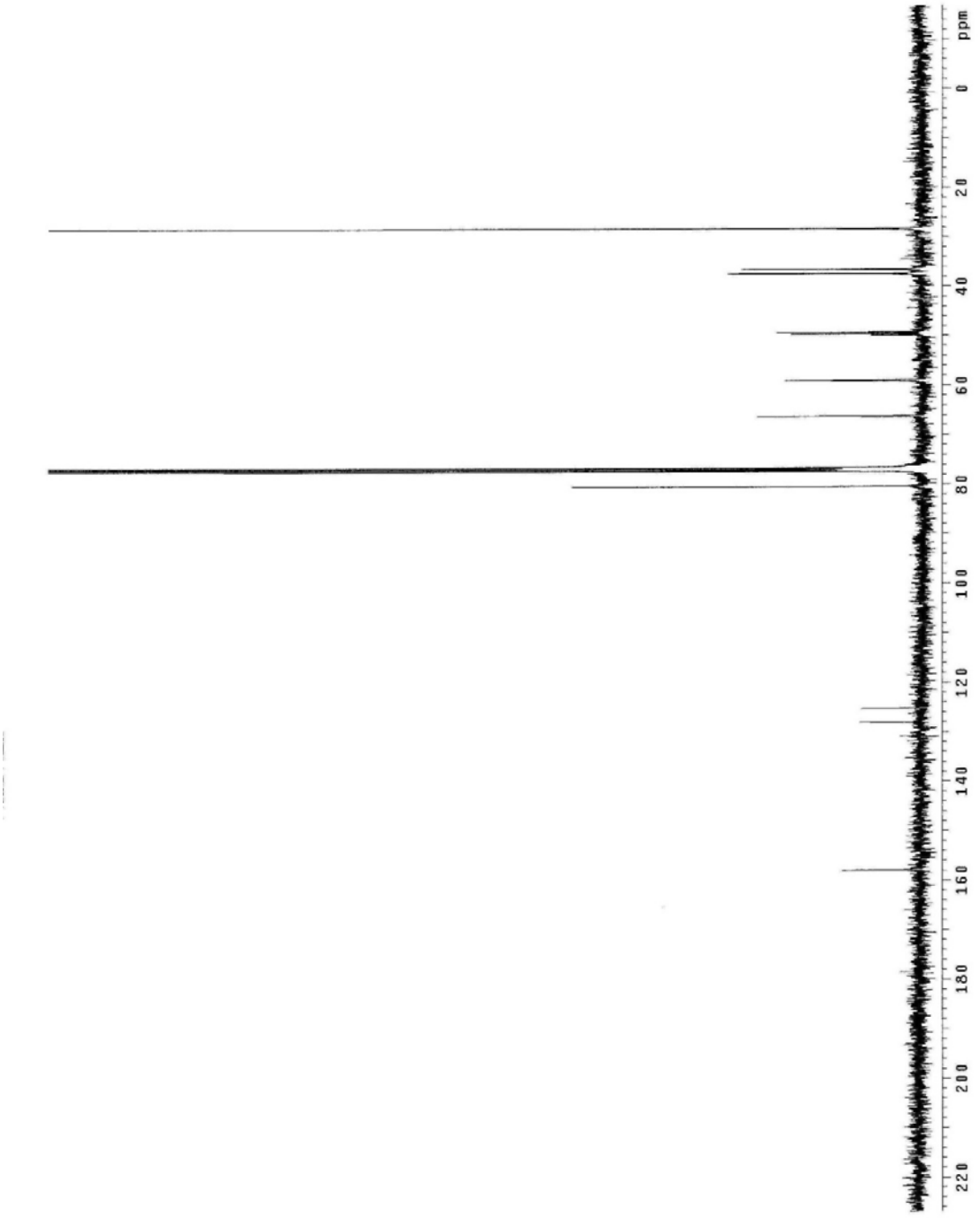
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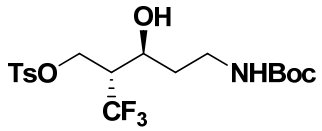
(*2R,3S*)-5-(*tert*-butoxycarbonylamino)-3-hydroxy-2-(trifluoromethyl)pentyl 4-methylbenzenesulfonate 3.5i



An oven-dried round bottom flask under atmosphere of N_2 was charged with *tert*-butyl (*3S,4R*)-5,5,5-trifluoro-3-hydroxy-4-(hydroxymethyl)pentylcarbamate **3.4i** (299 mg, 1.04 mmol, 100 mol%) and TsCl (337 mg, 1.77 mmol, 170 mol%). Pyridine (5 mL, 0.2 M) was added and the mixture was stirred at ambient temperature overnight. After all starting material consumped, the reaction mixture was diluted with 30 mL ethyl acetate, washed with saturated $CuSO_4$ solution to remove pyridine, and washed with brine. After removing the solvent, **3.5i** was obtained as a pale yellow oil in 99% yield and used without further purification.

TLC (SiO_2): R_f = 0.35 (ethyl acetate:hexanes, 1:2).

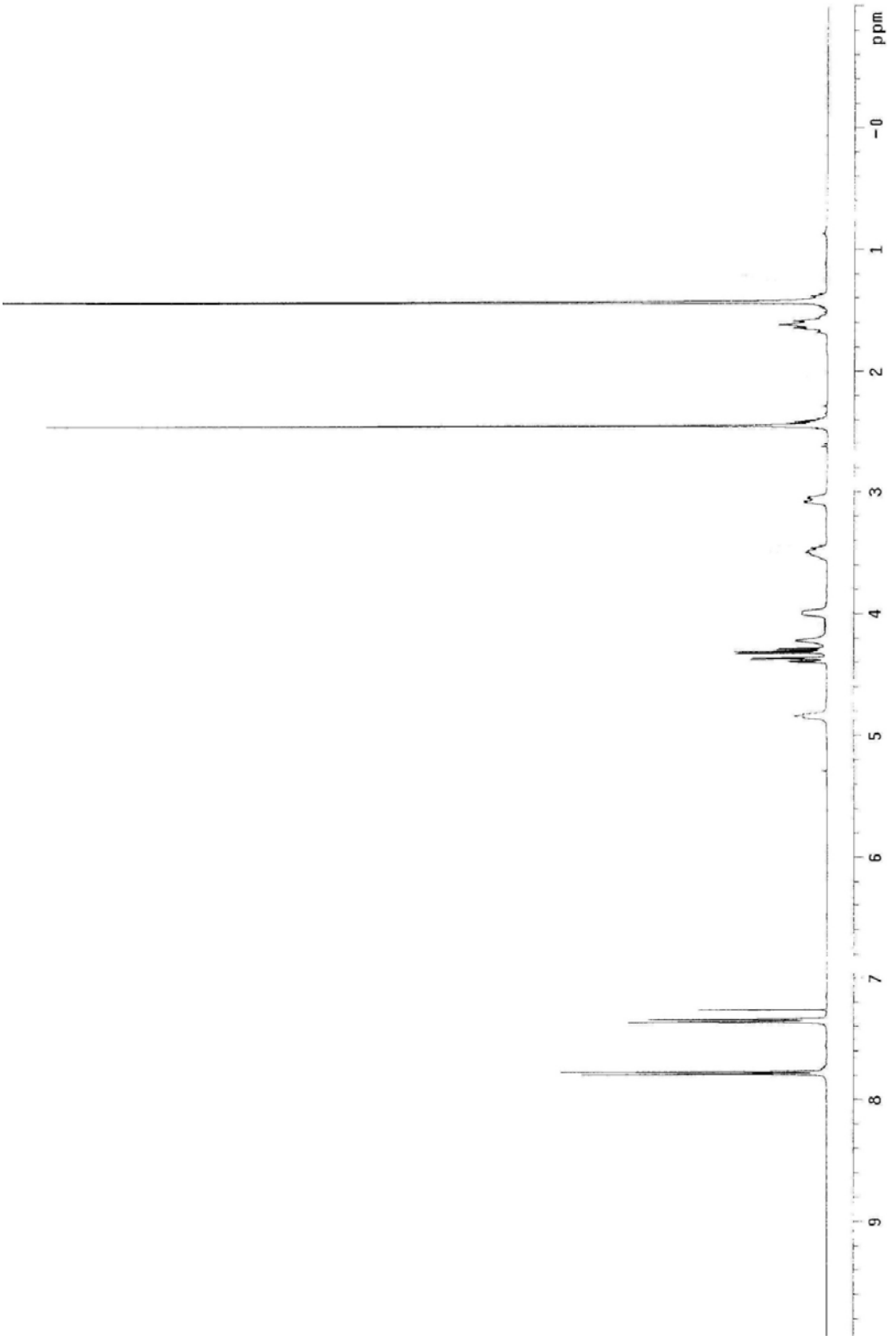
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.84 (br, 1H), 3.51-3.44 (m, 1H), 3.09-3.04 (m, 1H), 2.45 (s, 3H), 2.47-2.39 (m, 1H), 1.68-1.55 (m, 2H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8, 145.2, 132.2, 129.9, 128.0, 125.8 (q, *J* = 279.8 Hz), 80.3, 64.2, 63.2, 48.5 (q, *J* = 24.6 Hz), 36.5, 36.2, 28.2, 21.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ -66.62 (d, *J* = 9.0 Hz).

FTIR (neat): 3413, 2929, 1686, 1523, 1367, 1252, 1176, 1137, 984, 816, 664 cm^{-1}.

HRMS (CI) Calcd. for $C_{18}H_{27}NSO_6F_3$ $[M+H]^+$: 442.1511, Found: 442.1512.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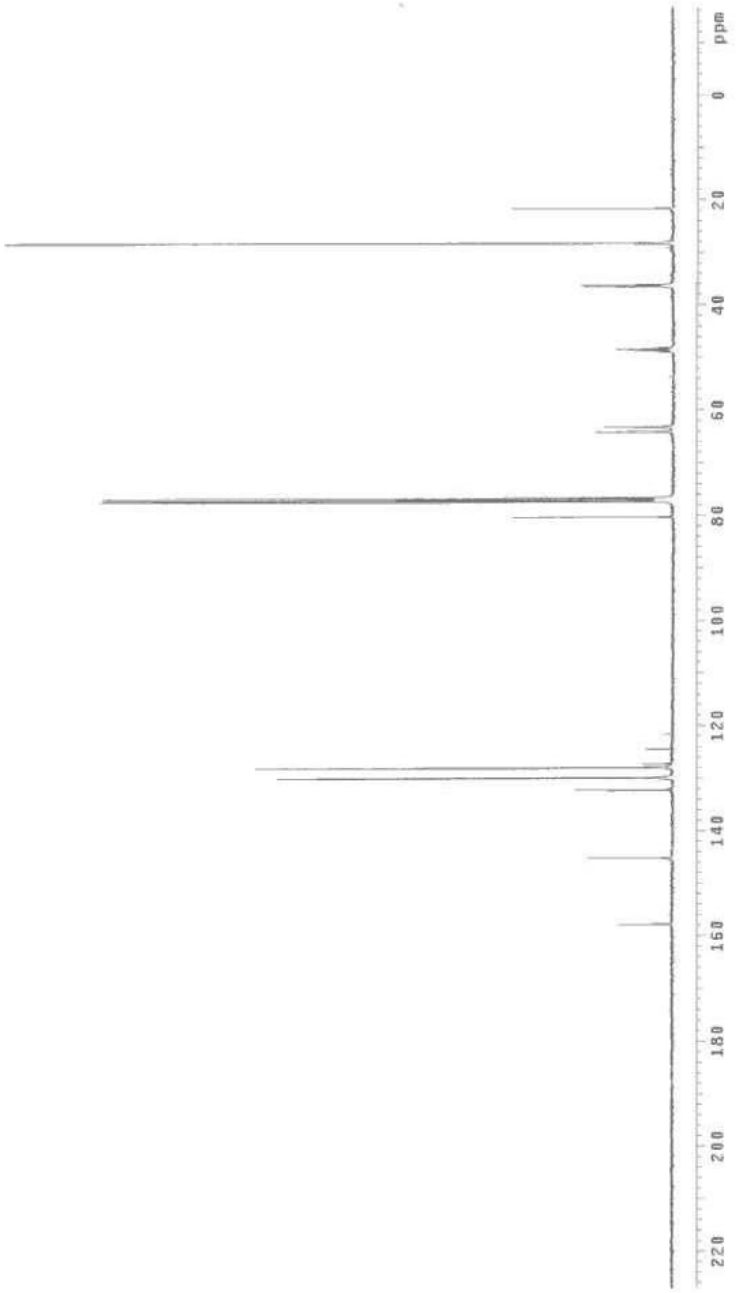
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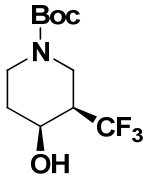
(*3R,4S*)-*tert*-butyl 4-hydroxy-3-(trifluoromethyl)piperidine-1-carboxylate 3.6



An oven-dried round bottom flask under atmosphere of N_2 was charged with **3.5i** (46.1 mg, 0.104 mmol, 100 mol%). Trifluoroacetic acid (0.5 mL, 0.2 M) was added and the mixture was stirred at ambient temperature for 15 minutes. After all starting material consumped, the reaction mixture was concentrated *in vacuo*. Acetonitrile (5 mL, 0.02 M) was added, and freshly distilled diisopropylethylamine (80.7 mg, 0.624 mmol, 600 mol%) was injected dropwisely. The reaction mixture was stirred at ambient temperature overnight, followed by adding di-*tert*-butyl dicarbonate (36.2 mg, 0.208 mmol, 200 mol%) and stirred fro another 8 hours. After removing the solvent, purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:4 with 0.1% TEA) provided **3.6** (22.7 mg, 0.084 mmol) as colorless oil in 81% yield.[18]

TLC (SiO_2): R_f = 0.45 (ethyl acetate:hexanes, 1:2).

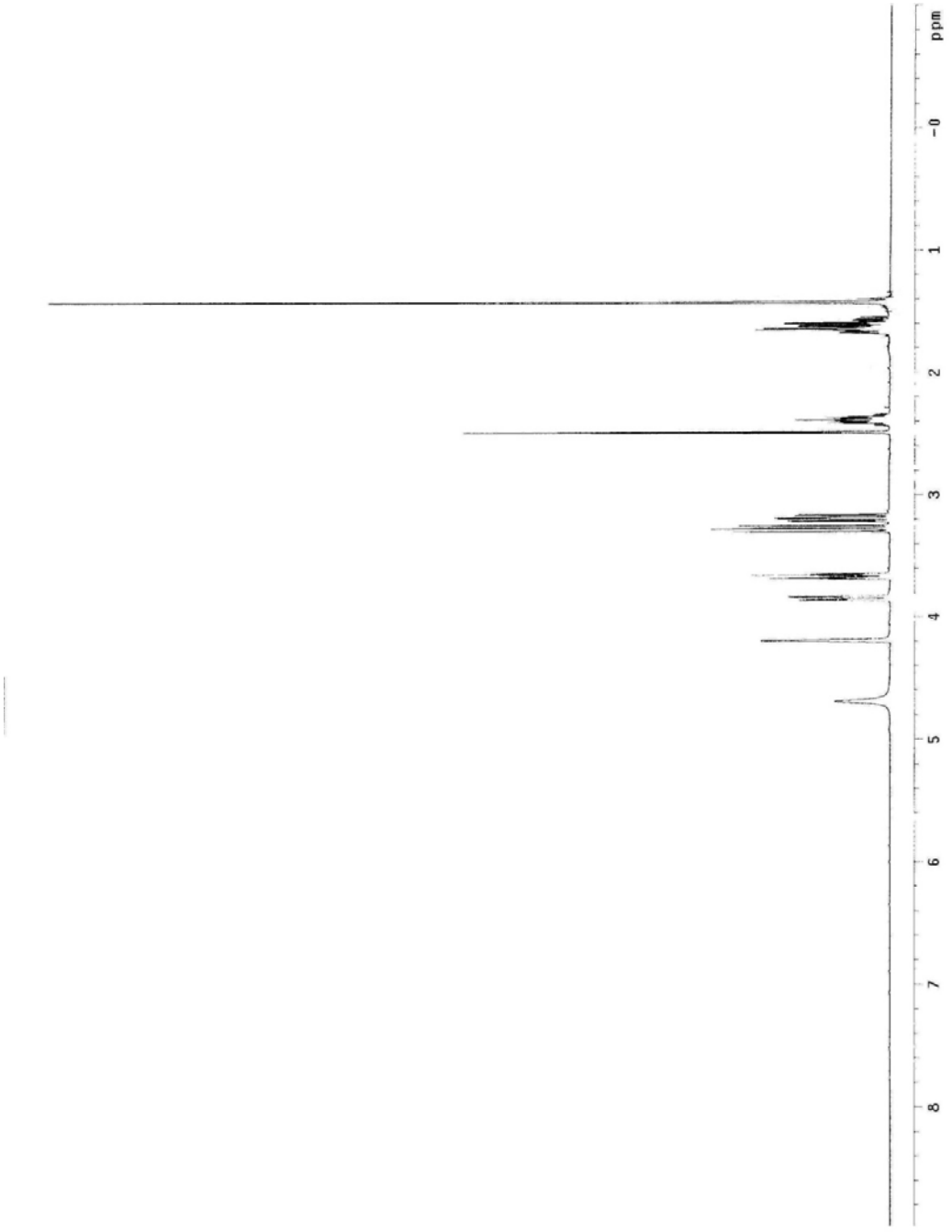
^{1}H NMR (500 MHz, DMSO, 120 ^{o}C): δ 4.69 (br, 1H), 4.20 (s, 1H), 3.84 (dd, *J* = 13.0, 4.0 Hz, 1H), 3.69-3.64 (m, 1H), 3.27 (dd, *J* = 13.0, 11.0 Hz, 1H), 3.19 (ddd, *J* = 13.5, 11.5, 3.5 Hz, 1H), 2.43-2.37 (m, 1H), 1.68-1.55 (m, 1H), 1.42 (s, 9H).

^{13}C NMR (125 MHz, DMSO, 120 ^{o}C): δ 153.4, 125.7 (q, *J* = 279.3 Hz), 78.5, 60.9 (q, *J* = 2.4 Hz), 43.7 (q, *J* = 23.8 Hz), 37.8, 37.2 (q, *J* = 2.8 Hz), 31.3, 27.5.

^{19}F NMR (470 MHz, DMSO, 120 ^{o}C): δ -66.61 (d, *J* = 9.4 Hz).

FTIR (neat): 3427, 2926, 1671, 1430, 1259, 1240, 1155, 1111, 1029, 862, 842, 797,706 cm^{-1}.

HRMS (CI) Calcd. for $C_{11}H_{18}NOF_3Na$ $[M+Na]^+$: 292.1133, Found: 292.1132.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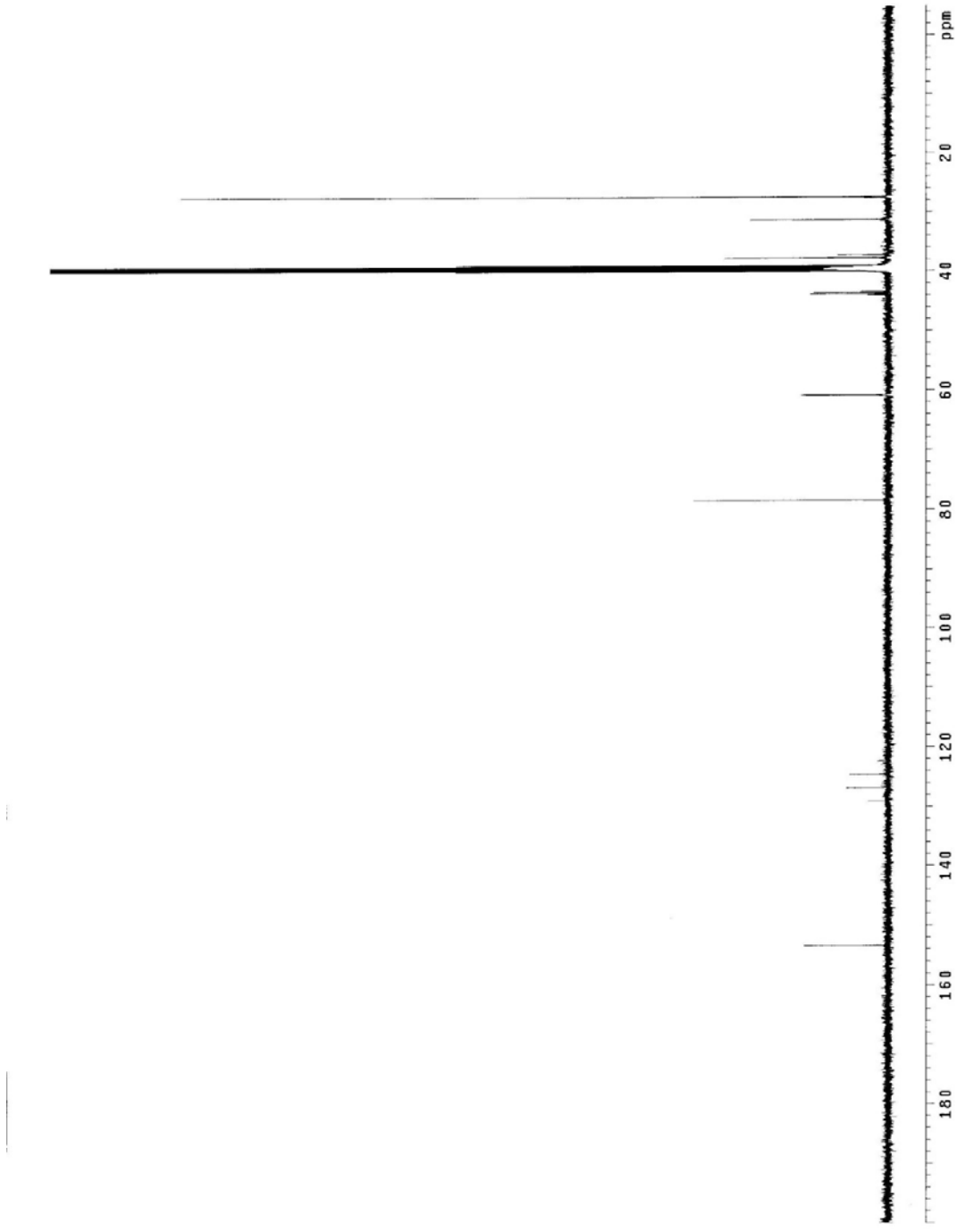
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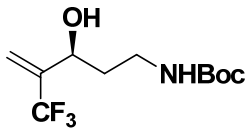
ppm

(*S*)-*tert*-butyl 3-hydroxy-4-(trifluoromethyl)pent-4-enylcarbamate 3.6a



An oven-dried round bottom flask under atmosphere of N_2 was charged with **3.5i** (44.1 mg, 0.1 mmol, 100 mol%). Freshly made NaOMe (1.0 M in MeOH, 0.5 mL, 0.2 M) was added under 0 ^oC and the mixture was stirred at ambient temperature overnight. After all starting material consumped, solvent was removed and the residue was extracted with 30 mL ethyl acetate, washed with brine, concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:3 with 0.1% TEA) provided (*S*)-*tert*-butyl 3-hydroxy-4-(trifluoromethyl)pent-4-enylcarbamate (24.8 mg, 0.094 mmol) as a colorless oil in 94% yield.

TLC (SiO_2): R_f = 0.5 (ethyl acetate:hexanes, 1:2).

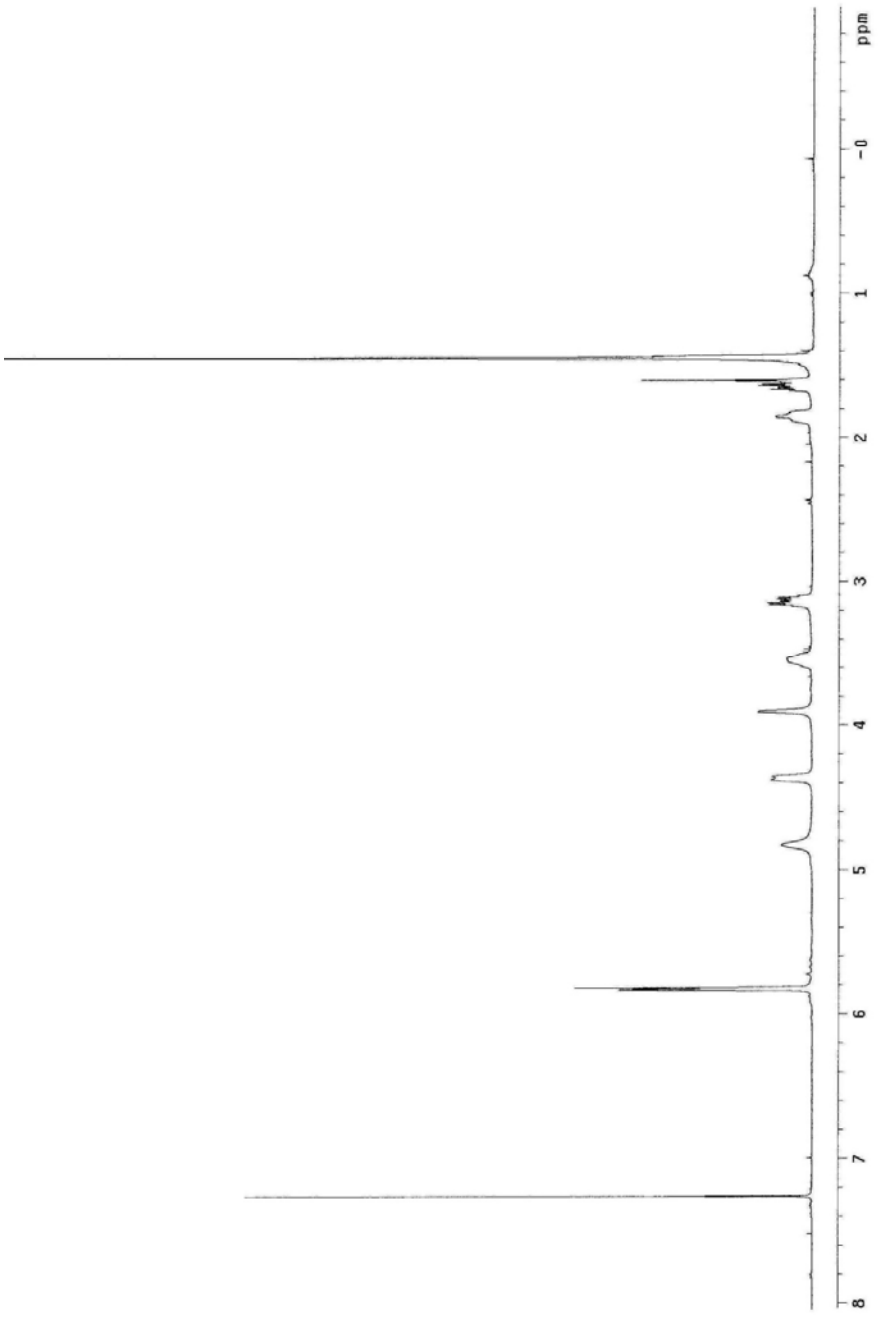
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83 (d, *J* = 0.8 Hz, 1H), 5.83-5.82 (m, 1H), 4.83 (br, 1H), 4.37 (d, *J* = 9.6 Hz, 1H), 3.91 (s, 1H), 3.56-3.54 (m, 1H), 3.17-3.10 (m, 1H), 1.88-1.82 (m, 1H), 1.67-1.61 (m, 1H), 1.45 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 141.1 (q, *J* = 29.0 Hz), 123.4 (q, *J* = 271.6 Hz), 118.8 (q, *J* = 5.9 Hz), 80.1, 65.5, 37.3, 36.8, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ -66.65.

FTIR (neat): 3345, 2979, 1685, 1516, 1368, 1280, 1165, 1122, 1086, 953, 863, 782 cm^{-1}.

HRMS (CI) Calcd. for $C_{11}H_{18}NOF_3Na$ $[M+Na]^+$: 292.1133, Found: 292.1133.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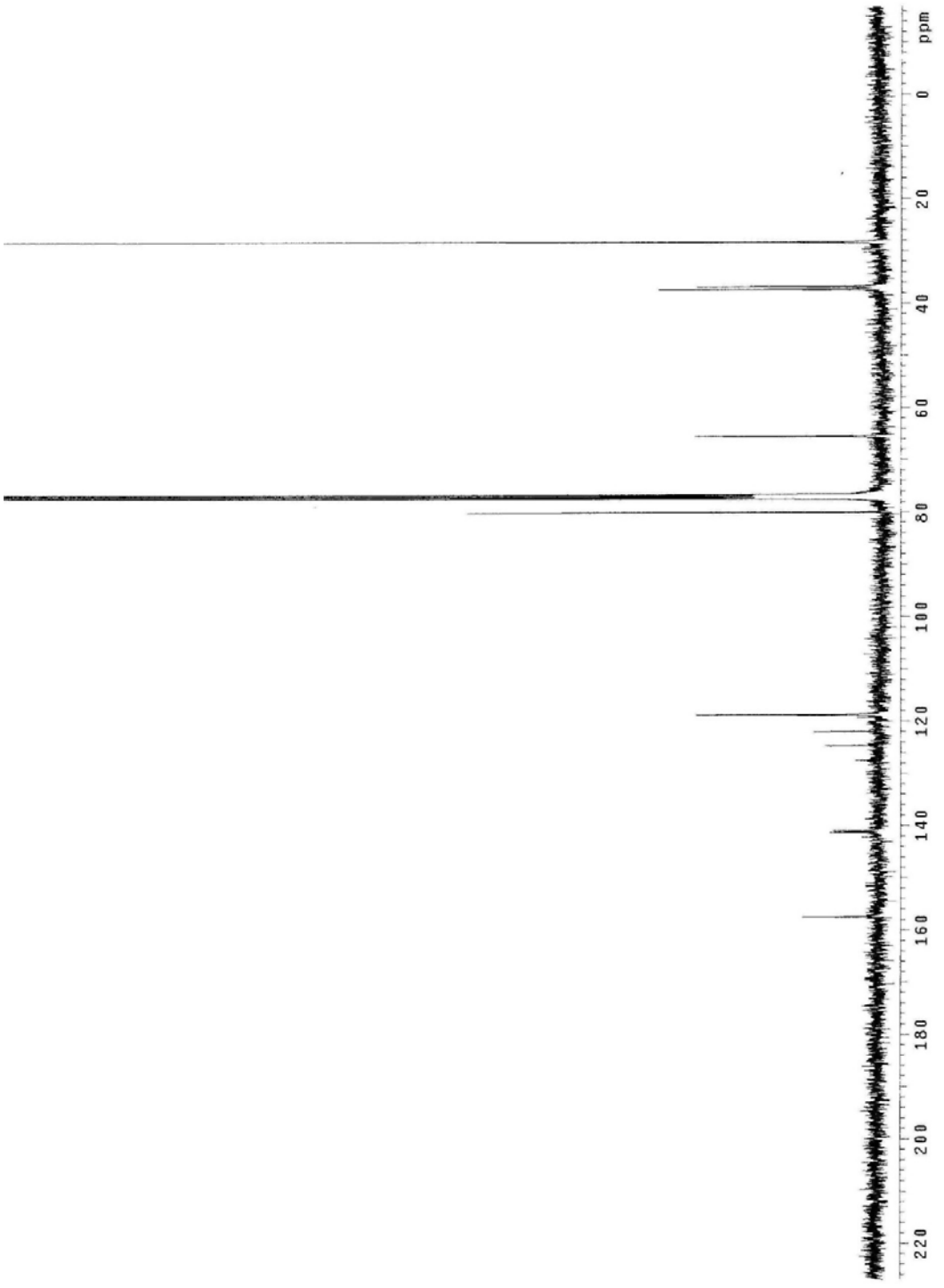
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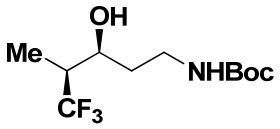
***tert*-butyl (*3S,4S*)-5,5,5-trifluoro-3-hydroxy-4-methylpentylcarbamate 3.7**



To a mixture of (*S*)-*tert*-butyl 3-hydroxy-4-(trifluoromethyl)pent-4-enylcarbamate (24.8 mg, 0.094 mmol, 100 mol%) and Ru(*rac*BINAP)$(OAc)_2$[19] (4.1mg, 0.005 mmol, 5 mol%) was added dry methanol (4 mL, 0.025 M) in autoclave and then the reaction mixture was stirred under an hydrogen pressure of 30 atm at room temperature overnight. After finishing the reaction, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (SiO_2; ethyl acetate: hexanes, 1:3 with 0.1% TEA) to afford **3.7** (24.9 mg, 0.086 mmol) as a colorless oil in 92% yield.[20]

TLC (SiO_2): R_f = 0.5 (ethyl acetate:hexanes, 1:2).

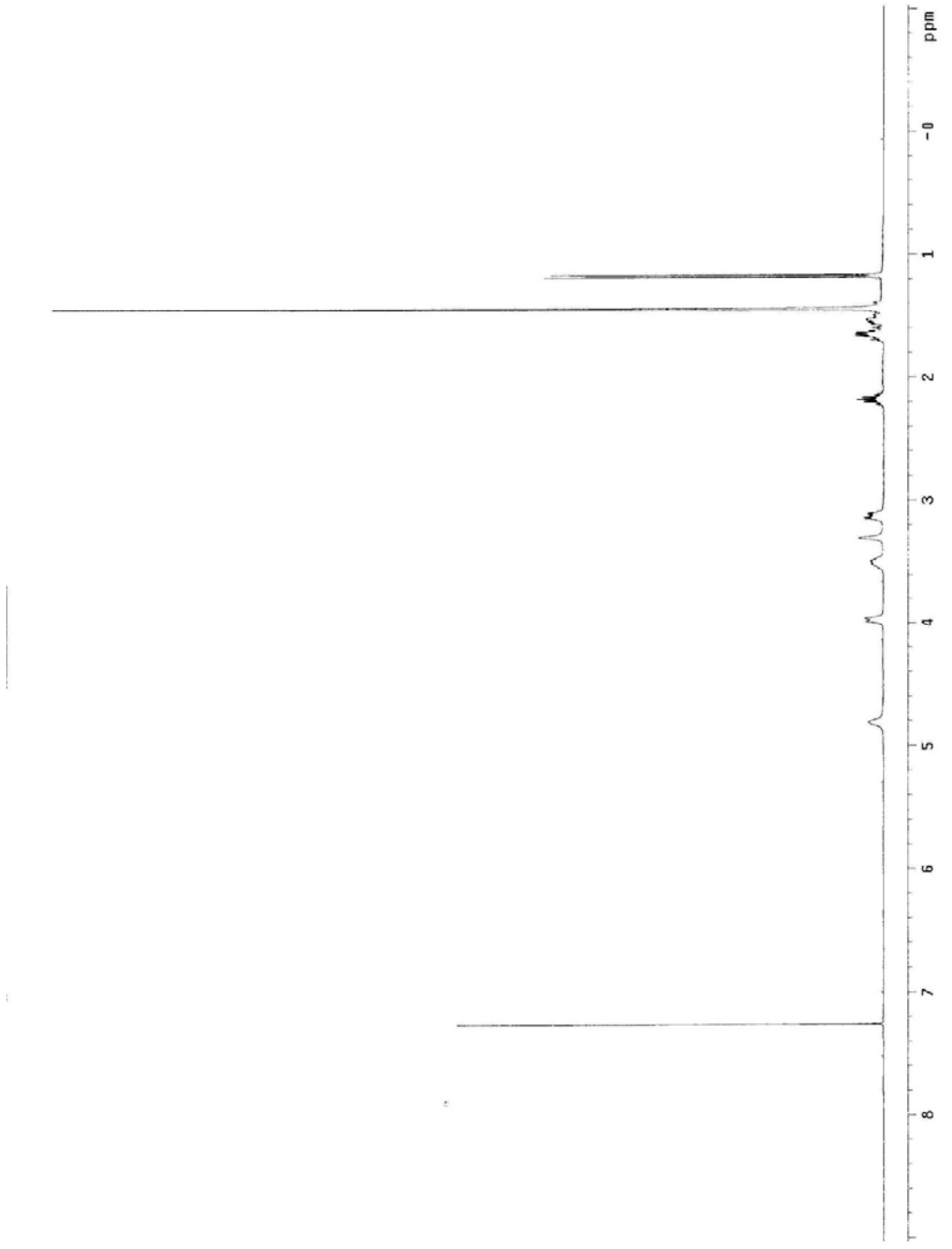
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.81 (br, 1H), 3.97 (d, *J* = 10.0 Hz, 1H), 3.52-3.47 (m, 1H), 3.30 (br, 1H), 3.16-3.10 (m, 1H), 2.22-2.14 (m, 1H), 1.70-1.46 (m, 1H), 1.44 (s, 9H), 1.18 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 127.8 (q, *J* = 279.0 Hz), 79.9, 65.8, 43.1 (q, *J* = 23.8 Hz), 37.1, 35.6, 28.3, 7.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ -70.06 (d, *J* = 9.6 Hz).

FTIR (neat): 3350, 2981, 2928, 1685, 1520, 1458, 1368, 1271, 1172, 1145, 1075, 1007, 861, 681 cm^{-1}.

HRMS (CI) Calcd. for $C_{11}H_{21}NOF_3Na$ $[M+H]^+$: 272.1474, Found: 272.1475.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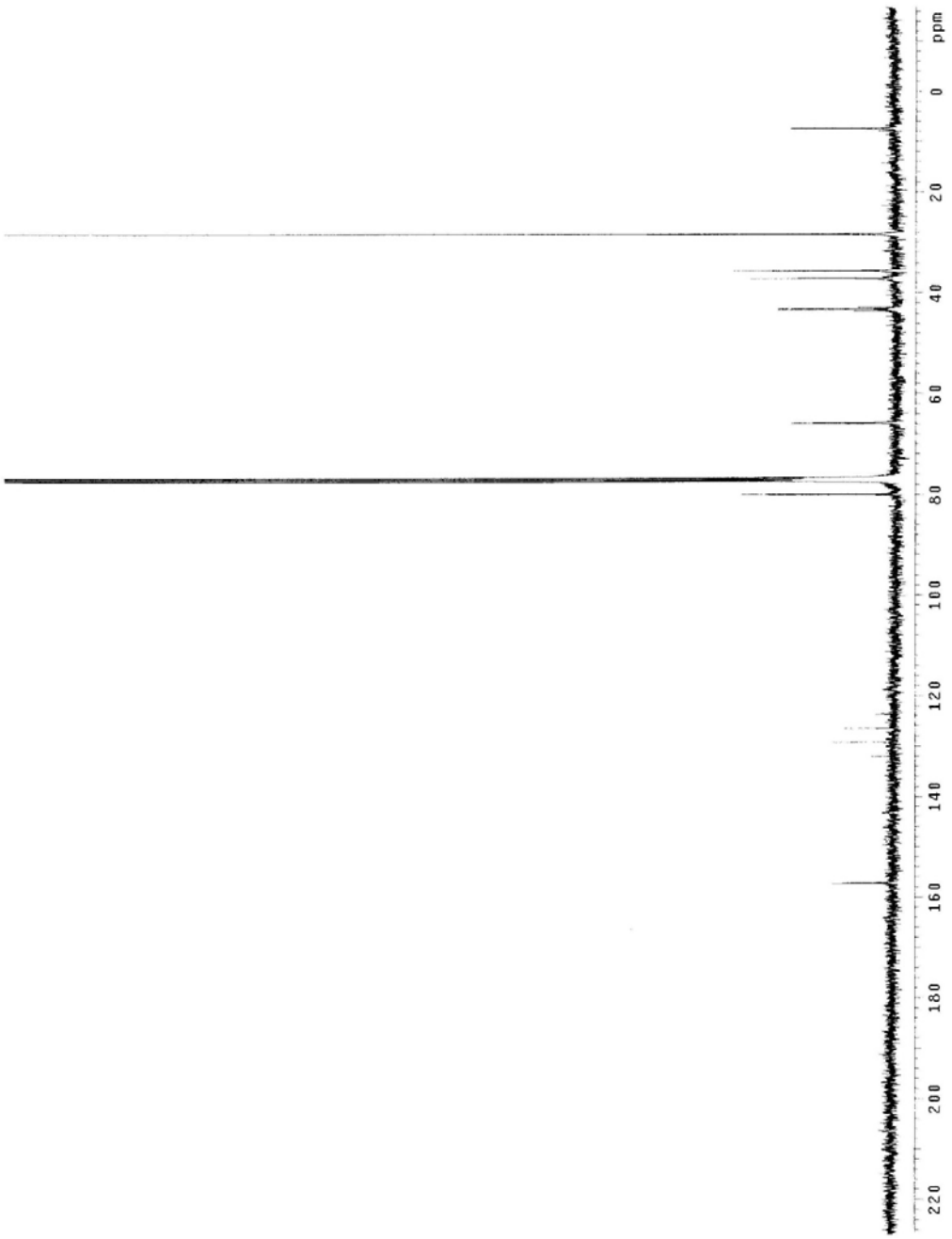
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ppm

CHAPTER 4: ENHANCED IRIDIUM CATALYZED CARBONYL CROTYLATION AND DOUBLE CROTYLATION: BEYOND STEPWISE CARBONYL ADDITION IN POLYKETIDE CONSTRUCTIONS[1]

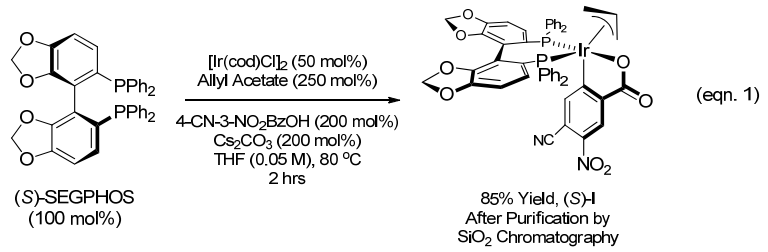
4.1 ENHANCED CARBONYL CROTYLATION USING ISOLABLE CATALYST[1a]

4.1.1 INTRODUCTION

In the course of developing C-C bond forming hydrogenations and transfer hydrogenations,[2] it was found that *ortho*-cyclometallated iridium *C,O*-benzoates serve as catalysts for diverse carbonyl allylation processes whereinprimary alcohol dehydrogenation triggers reductive generation of allyliridium nucleophiles from allylic carboxylates, thus enabling asymmetric carbonyl allylation directly from the alcohol oxidation level.Under nearly identical conditions, carbonyl allylation is achievedfrom the aldehyde oxidation level employing isopropanol as terminal reductant.[3] Notably, by harnessing the reductive capability of alcohol mediated transfer hydrogenation, asymmetric carbonyl allylationis achieved in the absence of stoichiometric allylmetal reagents or metallic reductants, representing a significant departure from conventional carbonyl allylation protocols.[4,5,6]

4.1.2 REACTION OPTIMIZATION

Our initial investigations into stereoselective carbonyl crotylation employing α-methyl allyl acetate as the crotyl donor were achieved using the *ortho*-cyclometallated iridium *C,O*-benzoateprepared *in situ*from $[Ir(cod)Cl]_2$, allyl acetate, 4-cyano-3-nitrobenzoic acid and the chiral phosphine ligand (*S*)-SEGPHOS.[3c,7,8] Although *in situ* assembly of the catalyst proved convenient and exceptional enantioselectivities typically wereobserved (>95% ee), only moderate levels of*anti*-diastereoselectivity were evident (5:1 – 11:1 dr). In subsequent work, conditions for preparation of thediscrete*ortho*-cyclometallated iridium *C,O*-benzoate precatalyst and its isolation via precipitation were identified.[3d] Notably, using such single component precatalysts, alcohol mediated carbonyl allylation processeswere found to proceed atconsiderably lower temperatures. This fact prompted the present reinvestigation of alcohol mediated carbonyl crotylation. Here, we report that the *ortho*-cyclometallated iridium *C,O*-benzoate derived from $[Ir(cod)Cl]_2$, allyl acetate, 4-cyano-3-nitrobenzoic acid and (*S*)-SEGPHOS, termed (*S*)-**I**, is subject to conventional silica gel flash chromatographic purification,and that use of (*S*)-**I** purified in this manner enableslow temperature (60 ^{o}C) alcohol mediated carbonyl crotylation, resulting in enhanced levels of *anti*-diastereo- and enantioselectivity. (eqn. 1)



(eqn. 1)

The performanceof the chromatographically isolated precatalyst (*S*)-**I** was evaluated inalcohol mediated carbonyl crotylation, which allows a comparison with

results obtained upon generation of (*S*)-**I** *in situ*.[3c] Whereas reaction temperatures of 90 ^{o}C were necessary using the catalyst generated *in situ*, use of the chromatographically isolated precatalyst (*S*)-**I** was possible at 60 ^{o}C without extending reaction time. Furthermore, use of the chromatographically isolated precatalyst (*S*)-**I** led to a considerable improvement the level of *anti*-diastereoselectivity (7:1 – > 20:1 dr), which was accompanied by a modest but consistent improvement in enantioselectivity. As demonstrated by the conversion of alcohols **4.1.2a**-**4.1.2i** to adducts **4.1.4a**-**4.1.4i** and the conversion of aldehydes **4.1.3a**-**4.1.3i** to adducts **4.1.4a**-**4.1.4i**, these favorable trends in selectivityevident in carbonyl crotylations from the alcohol or aldehyde oxidation level (Table 4.1).

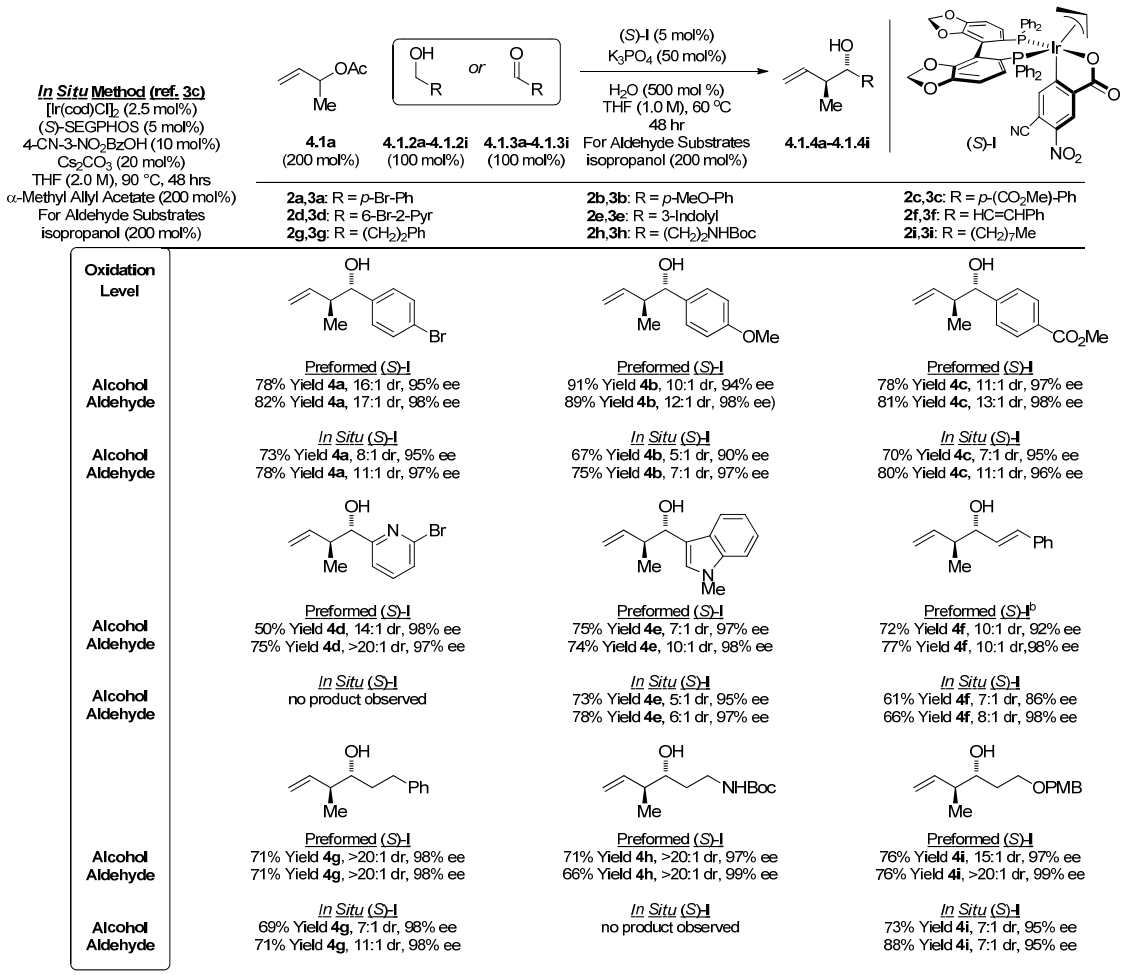


Table 4.1 Enhanced levels of *anti*-diastereo- and enantioselectivity in alcohol mediated carbonyl crotylationsemploying an isolable single component iridium catalyst

4.1.3 SUMMARY

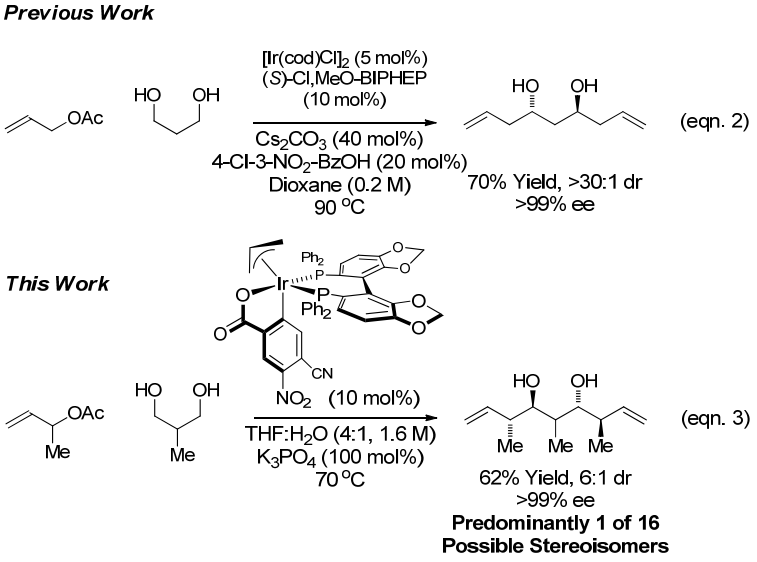
In summary, we reportthat the chromatographically isolated iridium precatalyst (*S*)-**I** promotes enhanced levels of *anti*-diastereo- and enantioselectivity in carbonyl crotylations from the alcohol or aldehyde oxidation level employing employing α-methyl allyl acetate as the crotyl donor.[3c] Future studies will focus on the development of related

C-C bondforming processes that occur in the absence of stoichiometric organometallic reagents, including butadiene-mediated carbonyl crotylations from the alcohol oxidation level.

4.2 DIRECT GENERATION OF POLYPROPIONATE STEREOPOLYADS VIA DOUBLE CROTYLATIONS: BEYOND STEPWISE CARBONYL ADDITION IN POLYKETIDE CONSTRUCTION[1b]

4.2.1 INTRODUCTION

The complex issues of stereoselectivity posed by polyketide natural products are most often addressed through stepwise carbonyl addition reactions involving use of chiral auxiliaries, chiral reagents and premetallated nucleophiles.[9,10] In the course of studies on hydrogen-mediated C-C bond formation,[11] hydrogen exchange between primary alcohols and π-unsaturated reactants was found to trigger generation of electrophile-nucleophile pairs that combine to form products of carbonyl addition directly from the alcohol oxidation level.[12,13,14] A significant outcome of this approach resides in the ability to rapidly assemble polyacetate substructures through asymmetric double allylations of 1,3-diols (eqn. 2), as illustrated in dramatically simplified syntheses of the bryostatin A-ring[15a] and oxopolyene macrolide roxaticin.[15d]



Corresponding double crotylations would enable direct generation of pseudo-C_2-symmetric[16] polypropionate stereoquintets (eqn. 2), which appear as substructures in diverse polyketide natural products, including rifamycin,[17] swinholide,[18] scytophycin,[19] saliniketal[20] and reidispongiolide[21] (Figure 4.1). However, attempted double crotylations employing the catalyst generated *in situ* from $[Ir(cod)Cl]_2$, 4-cyano-3-nitrobenzoic acid, allyl acetate and (*R*)-SEGPHOS were unsuccessful. Recently, we observed that chromatographic isolation of the iridium precatalyst allows alcohol mediated carbonyl crotylations to be conducted at significantly lower temperature, resulting in enhanced levels of *anti*-diastereo- and enantioselectivity.[1a] More significantly, the chromatographically purified precatalyst enables carbonyl crotylations that are not possible under previously reported conditions involving *in situ* generation of the precatalyst.

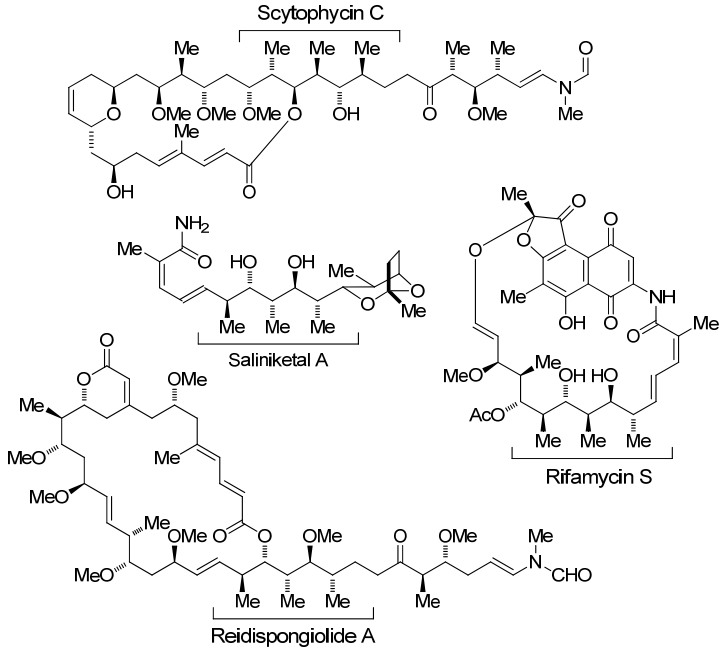
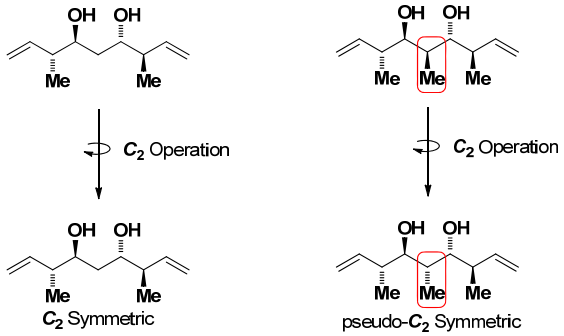


Figure 4.1 Representative polyketide natural products possessing pseudo-C_2-symmetric polypropionate stereoquintets.



Given these findings, the generation of polypropionate stereoquintets using *anti*-diastereo- and enantioselective carbonyl double crotylation of 1,3-diols was revisited. Here, we report that exposure of α-methyl allyl acetate to 1,3-propanediols **4.2.1a** or **4.2.1b** in the presence of the chromatographically purified iridium precatalyst (*R*)-**I** results in double carbonyl crotylation from the diol oxidation level to deliver the C_2-

symmetric stereopolyads **4.2.2a** and **4.2.3a**, respectively, with exceptional control of *anti*-diastereo- and enantioselectivity. *The present double crotylation process has no counterpart in conventional crotylmetal chemistry and is unique in its ability to generate acyclic stereoquintets from achiral reactants with control of relative and absolute stereochemistry*.[22,23,24]

To illustrate the utility of this methodology *vis-à-vis* polyketide construction, syntheses of key polypropionate substructures were executed with dramatic enhancement in step economy. Specifically, the *ansa* chain of rifamycin S spanning C19-C27 was prepared in 8 steps *versus* 26 steps, as described by Kishi.[16c-e] Additionally, the scyotphycin C19-C25 stereoquintet was prepared 8 steps *versus* 15 steps, as described by Miyashita.[18h,i]

4.2.2 RESULTS AND DISCUSSION

Enantioselective double crotylation of 1,3-propanediol **4.2.1a** potentially generates as many as ten stereoisomers. Hence, quantitative evaluation of the product distribution represents a formidable challenge. A calculation of the theoretical distribution of stereoisomers based on a 99:1 enantiomeric ratio and 15:1 diastereomeric ratio (*anti*:*syn*) predicts a diastereomeric ratio of 6.2:1 dr (**4.2.2a** versus all other stereoisomers combined) (Figure 4.2).

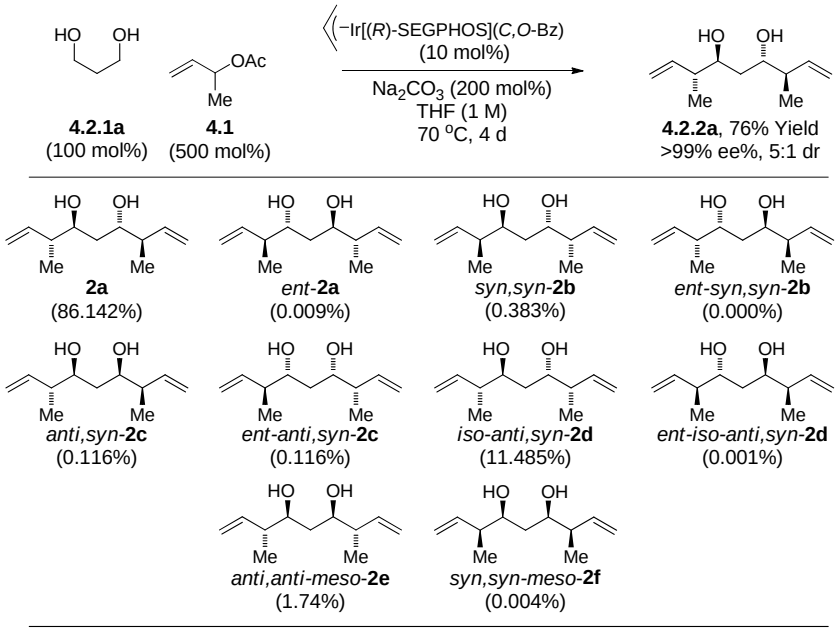
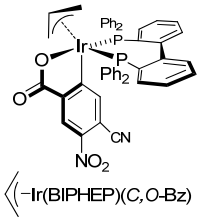


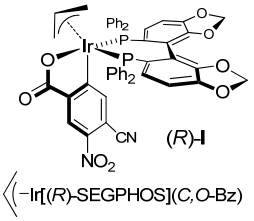
Figure 4.2 Calculated theoretical distribution of stereoisomers obtained in the double crotylation of 1,3-propanediol **4.2.1a** based on 98% ee for both *syn*- and *anti* -crotylation events and a 15:1 dr (*anti*:*syn*) and observed experimental results.

To quantitatively evaluate product distributions obtained in the course of optimization, authentic samples of **4.2.2a**, *ent*-**4.2.2a**, *anti,anti-meso*-**4.2.2e** were prepared in a conventional stepwise manner involving successive mono-crotylation.[25] Authentic samples of *anti,syn*-**4.2.2c** and *rac-iso-anti,syn*-**4.2.2d** were prepared conveniently *via* Mitsunobu inversion of **4.2.2a** and *anti,anti-meso*-**4.2.2e**, respectively. These authentic standards were analyzed by chiral stationary phase GC and a comparison to the reaction mixture obtained upon exposure of 1,3-propanediol **4.2.1a** to α-methyl allyl acetate in the presence of the iridium catalyst derived from $[Ir(cod)Cl]_2$, allyl acetate, 4-cyano-3-nitrobenzoic acid, and the chelating phosphine ligand BIPHEP (2,2'-

bis(diphenylphosphino)biphenyl), as well as the product distribution obtained using the chromatographically purified chiral complex modified by (*R*)-SEGPHOS, termed (*R*)-**I**.



〈–Ir(BIPHEP)(*C,O*-Bz)



(*R*)-**I**

〈–Ir[(*R*)-SEGPHOS](*C,O*-Bz)

For the reaction mixture obtained using the BIPHEP-modified catalyst, chiral stationary phase GC analysis reveals ten distinct species, presumably the ten stereoisomers indicated in Figure 4.2. Indeed, good correlation in GC retention time is observed with the six authentic samples of **4.2.2a**, *ent*-**4.2.2a**, *anti,syn*-**4.2.2c**, *anti,anti-meso*-**4.2.2e**, *iso-anti,syn*-**4.2.2d** and *ent-iso-anti,syn*-**4.2.2d**. A dramatic simplification in product distribution is observed in the enantioselective reaction employing the chiral catalyst (*R*)-**I**.[26] Chiral stationary phase GC and ^{1}H NMR analysis reveal only two stereoisomers: the C_2-symmetric adduct **4.2.2a** and a minor stereoisomer identified as *iso-anti,syn*-**4.2.2d**. These data are in excellent agreement with the predicted stereoisomeric ratios. Isolation by silica gel chromatography delivers **4.2.2a** in 76% yield as a single enantiomer as a 5:1 mixture of diastereomers. Thus, an acyclic array of four stereogenic centers is generated in a single manipulation from achiral reactants with control of relative and absolute stereochemistry (Figure 4.3).

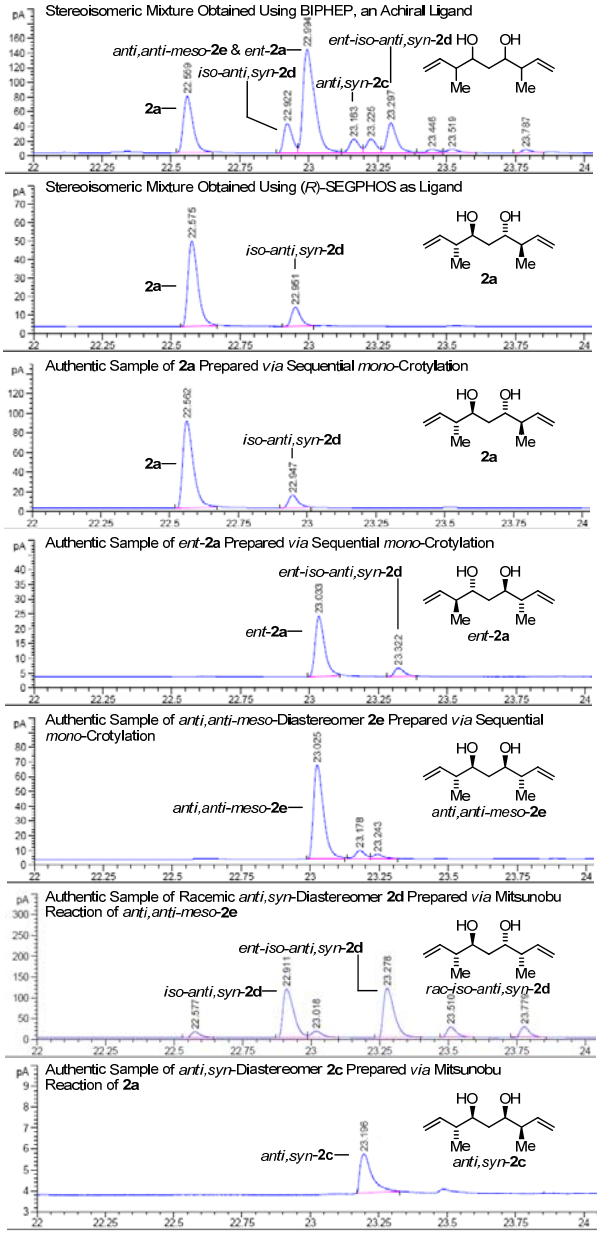


Figure 4.3 Characterization of the product distribution obtained upon *anti*-upon diastereo- and enantioselective double *C*-crotylation of 1,3-propanediol **4.2.1a**.

Given these favorable results, the double crotylation of 2-methyl-1,3-propanediol **4.2.1b** was explored. Here, generation of the pseudo-C_2-symmetric contiguous

polypropionate stereoquintet **4.2.3a** is potentially achieved in a single manipulation. However, sixteen stereoisomeric adducts may arise (Figure 4.4). The calculated theoretical distribution of stereoisomers obtained upon use of the chiral catalyst (*R*)-**I** suggests only three stereoisomers will be generated in significant proportion: the desired pseudo-C_2-symmetric adduct **4.2.3a** (86.1%), *s,s,a,a*-**4.2.3b** (5.7%) and *s,a,s,a*-**4.2.3b** (5.7%). Accordingly, authentic samples of these components and *ent*-**4.2.3a** were prepared in a conventional stepwise manner involving successive mono-crotylation.[24]

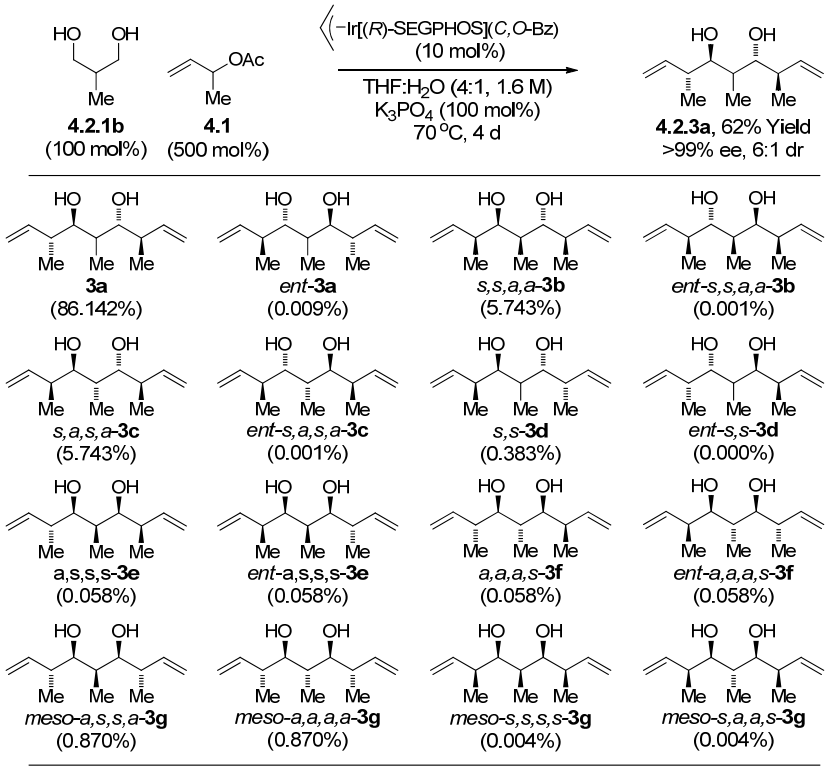


Figure 4.4 Calculated theoretical distribution of stereoisomers obtained in the double crotylation of 2-methyl propanediol **4.2.1b** based on 98% ee for both *syn*- and *anti* -crotylation events and a 15:1 dr (*anti*:*syn*) and observed experimental results.

Chiral stationary phase GC analysis of the mixture obtained in the double crotylation of 2-methyl-1,3-propanediol **4.2.1b** using the BIPHEP-modified catalyst reveals over ten distinct species. However, chiral stationary phase GC and ^{1}H NMR analysis of the reaction mixture obtained using chiral catalyst (*R*)-**I** reveals that the desired pseudo-C_2-symmetric adduct **4.2.3a** is formed predominantly, along with small quantities of *s,s,a,a*-**4.2.3b** and *s,a,s,a*-**4.2.3b** (Figure 4.5). This outcome is in excellent agreement with the predicted stereoisomeric ratios. Isolation by silica gel chromatography delivers **4.2.3a** in 62% yield as a single enantiomer as a 6:1 mixture of diastereomers. Thus, a contiguous acyclic array of five stereogenic centers is generated in a single manipulation from achiral reactants with control of relative and absolute stereochemistry (Figure 4.4).

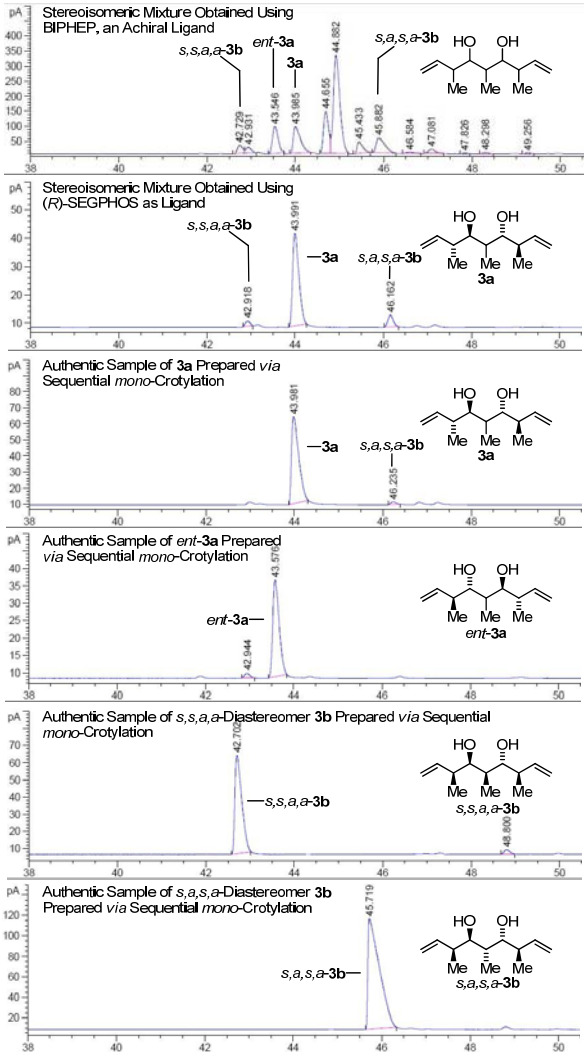
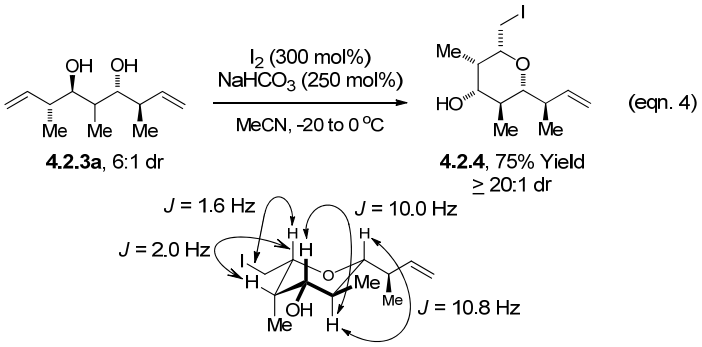


Figure 4.5 Characterization of the product distribution obtained upon *anti*-upon diastereo- and enantioselective double *C*-crotylation of 2-methyl-1,3-propanediol **4.2.1b**.

4.2.3 FORMAL SYNTHESIS OF RIFAMYCIN S AND SYNTHESIS OF THE SCYTOPHYCIN STEREOQUINTET

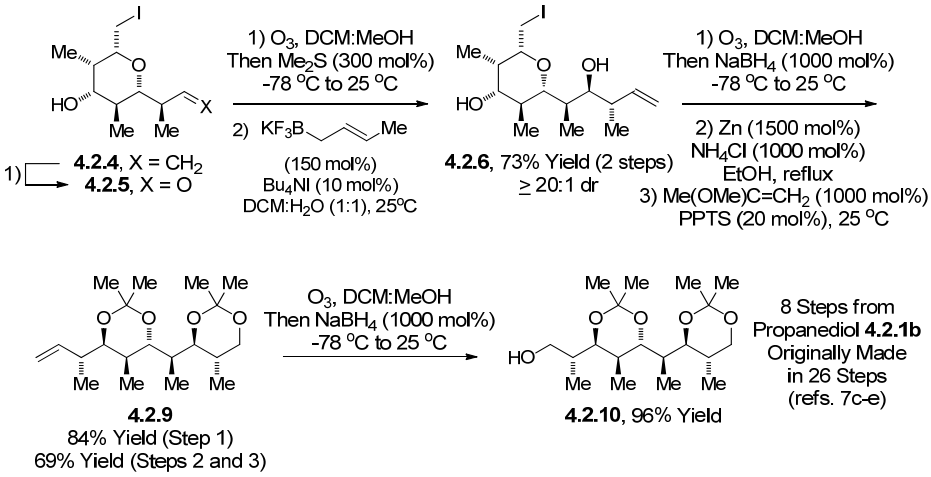
To explore the utility this methodology in polyketide construction, the product of double crotylation **4.2.3a** was applied in a synthetic approach to the *ansa* chain of rifamycin S, the C19-C27 stereoheptad. A key objective involves differentiation of the

homotopic hydroxyl moieties and olefinic termini of **4.2.3a**. Additionally, the latent stereocenter residing on the C_2-plane must be defined. These goals are achieved in a single operation through the conversion of **4.2.3a** to iodoether **4.2.4**. As corroborated by ^{1}H NMR analysis of the pyran spin system, the substituents attached to the two newly formed stereocenters of iodoether **4.2.4** are equatorially disposed (eqn. 4).



Elaboration of iodoether **4.2.4** to the *ansa* chain of rifamycin S is accomplished in a straightforward manner. Ozonolytic cleavage of iodoether **4.2.4** delivers the aldehyde **4.2.5**, which is subjected to Batey's crotylation conditions[27] to furnish the homoallylic alcohol **4.2.6** as a single stereoisomer (>20:1 dr), as determined by ^{1}H NMR analysis. Here, synergistic 1,2- and 1,3-asymmetric induction associated with the α- and β-stereocenters of the aldehyde, as described by the Felkin-Anh[28] and Cram-Reetz[29] models, respectively, account for the high level of stereoselectivity.[30] Ozonolytic cleavage of the terminal olefin followed by $NaBH_4$-mediated reduction of the ozonide delivers the primary alcohol **4.2.7** (not shown). Exposure of **4.2.7** to zinc dust in the presence of ammonium chloride induces β-iodoether cleavage to reveal the polypropionate stereohepted **4.2.8** (not shown). Conversion of tetraol **4.2.8** to the *bis*-acetonide **4.2.9** and finally, ozonolytic cleavage of the terminal olefin, again with

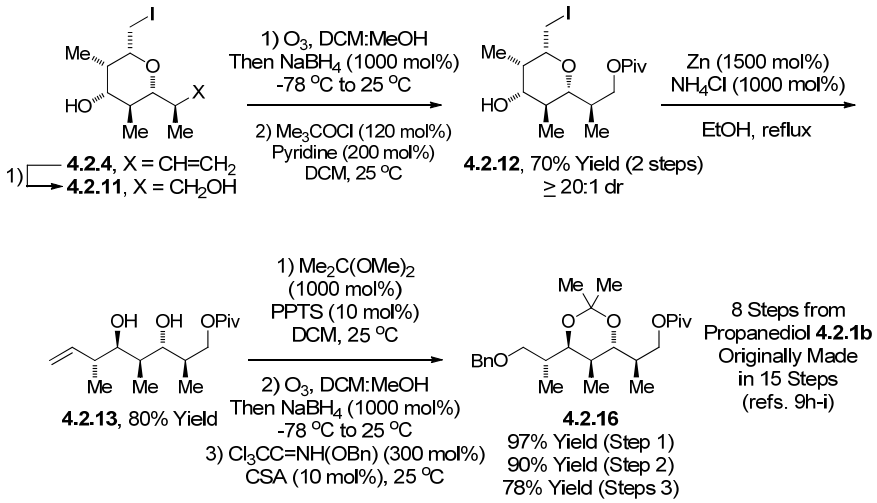
quenching of the ozonide by $NaBH_4$, delivers the protected C19-C27 stereohepted **4.2.10**, which is identical in all respects to previously reported material.[15] Preparation of the *ansa* chain in this manner constitutes a formal total synthesis of rifamycin S in 8 steps from 2-methyl-1,3-propanediol **4.2.1b** (Scheme 4.1).



Scheme 4.1 Formal synthesis of rifamycin S via construction of the C19-C27 stereoheptad.

To further illustrate the generality of this approach, a synthesis of the scyotphycin C C19-C25 stereoquintet was undertaken. Ozonolytic cleavage of the terminal olefin of iodoether **4.2.4** with $NaBH_4$-mediated reduction of the ozonide delivers the primary alcohol **4.2.11** (not shown), which is converted to the pivalate **4.2.12**. Exposure of an ethanolic solution of **4.2.12** to zinc dust in the presence of ammonium chloride induces β-iodoether cleavage to reveal the polypropionate stereoquintet **4.2.13**. Conversion of the diol to the acetonide followed by ozonolytic cleavage of the terminal olefin, again with quenching of the ozonide by $NaBH_4$, delivers the primary alcohol **4.2.15** (not shown),

which is converted to the benzylic ether **4.2.16** (Scheme 1). Ether **4.2.16** is identical in all respects to previously reported material.[17h-i]



Scheme 4.2 Synthesis of the scytophycin C C19-C25 stereoquintet.

4.2.4 SUMMARY

In summary, we report a powerful new process for the direct generation of polypropionate stereoquintets *via* iridium catalyzed *anti*-diastereo- and enantioselective carbonyl double crotylation of 1,3-propanediols **4.2.1a** and **4.2.1b**. Based on this methodology, syntheses of the rifamycin S C19-C27 stereoheptad and the scytophycin C C19-C25 stereoquintet were executed with dramatic enhancement in step economy. To our knowledge, the efficiency associated with the conversion of the achiral/chiral racemic materials **4.2.1b** and α-methyl allyl acetate to stereoquintet **4.2.3a** is without precedent. Future studies will focus on the development and application of other alcohol C-C couplings of relevance to polyketide construction.

4 .5 EXPERIMENTAL SECTION

General Methods

All reactions were run under an atmosphere of Argon. Tetrahydrofuran (THF) and toluene were obtained from Pure-Solv MD-5 Solvent Purification System (Innovative Technology). Anhydrous solvents were transferred by an oven-dried syringe. Sealed tubes (13x100 mm) were purchased from Fischer Scientific and were dried in an oven overnight and cooled under a stream of nitrogen prior to use. Commercially available allyl acetate (Aldrich) was purified by distillation prior to use. Cesium carbonate was purchased from Alfa Aesar and was used directly without further purification. Isopropanol (Fisher) was purified by distillation prior to use. Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F_{254}). Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M or M-H) or a suitable fragment ion. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) spectra were recorded with a Varian Gemini (400 MHz) spectrometer for $CDCl_3$ solutions and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δ_H (7.26 ppm) and $CDCl_3$ δ_C (77.0 ppm), respectively, as internal standards. Coupling constants are reported in Hertz (Hz).

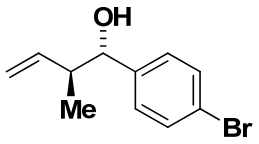
Preparation of (*R*)-I

To a mixture of $[Ir(cod)Cl]_2$ (87.3 mg, 0.13 mmol, 100 mol%), (*S*)-SEGPHOS (159 mg, 0.26 mmol, 200 mol%), Cs_2CO_3 (169 mg, 0.52 mmol, 400 mol%), 4-CN-3-NO_2BzOH (100 mg, 0.52 mmol, 400 mol%) and allyl acetate (65 mg, 0.65 mmol, 500 mol%) in a sealed tube under an atmosphere of N_2 was added THF (2.6 mL, 0.05 M). The reaction mixture was stirred for 30 minutes at ambient temperature and heated for 1.5 hours at 80 ^oC. Upon cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (10 mL), filtered through a celite plug, washed with CH_2Cl_2 (50 mL) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 20% Et_2O/CH_2Cl_2) and concentrated *in vacuo*. The light yellow gum was dissolved in THF (3 mL). Rapid addition of hexanes (50 mL) to the stirred solution resulted in precipitation of a bright yellow powder, which was collected by gravity filtration. Removal of trace solvents *in vacuo* delivered (*S*)-**I** (228 mg, 0.221 mmol) in 85% yield.

Preparation of (*S*)-I

To a mixture of $[Ir(cod)Cl]_2$ (87.3 mg, 0.13 mmol, 100 mol%), (*S*)-SEGPHOS (159 mg, 0.26 mmol, 200 mol%), Cs_2CO_3 (169 mg, 0.52 mmol, 400 mol%), 4-CN-3-NO_2BzOH (100 mg, 0.52 mmol, 400 mol%) and allyl acetate (65 mg, 0.65 mmol, 500 mol%) in a sealed tube under an atmosphere of N_2 was added THF (2.6 mL, 0.05 M). The reaction mixture was stirred for 30 minutes at ambient temperature and heated for 1.5 hours at 80 ^oC. Upon cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (10 mL), filtered through a celite plug, washed with CH_2Cl_2 (50 mL) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 20% Et_2O/CH_2Cl_2) and concentrated *in vacuo*. The light yellow gum was dissolved in THF (3 mL). Rapid addition of hexanes (50 mL) to the stirred solution resulted in precipitation of a bright yellow powder, which was collected by gravity filtration. Removal of trace solvents *in vacuo* delivered (*S*)-**I** (228 mg, 0.221 mmol) in 85% yield.

(*1S*,*2S*)-1-(4-bromophenyl)-2-methylbut-3-en-1-ol 4.1.4a



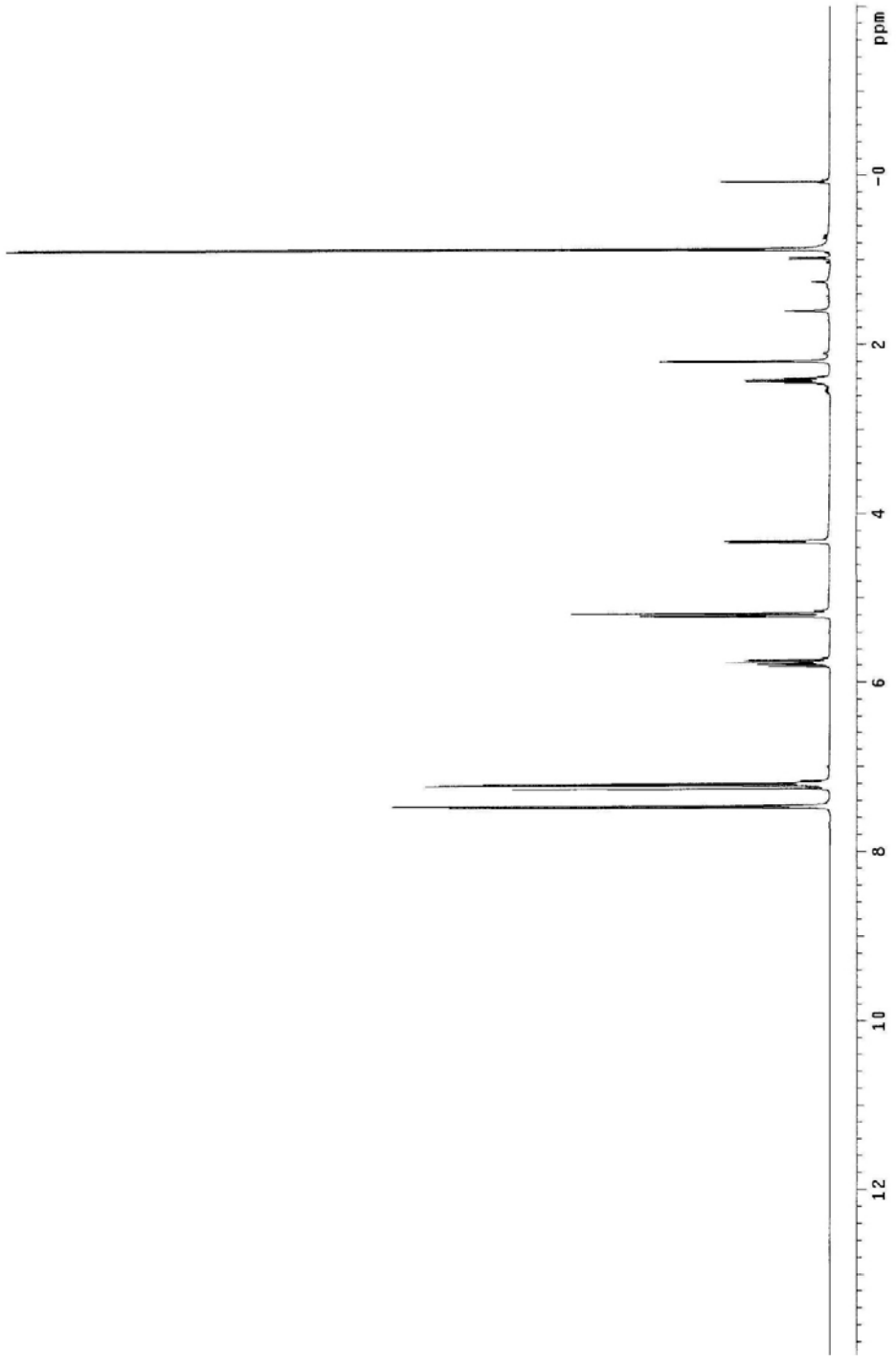
An oven-dried sealed tube under an atmosphere of N_2 was charged with (4-bromophenyl)methanol **4.1.2a** (37.4 mg, 0.20 mmol, 100 mol%), (*S*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (21.5 mg, 0.10 mmol, 50 mol%), THF (0.1 mL, 2.0 M), and H_2O (18 μL, 1.0 mmol, 500 mol%). But-3-en-2-yl acetate **4.1** (45.6 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 60 ^oC and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **4.1.4a** (37.6 mg, 0.156 mmol) as a colorless oil in 78% yield (16:1 dr).

TLC (SiO_2): R_f = 0.4 (ethyl acetate: hexanes, 1:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 5.81-5.71 (m, 1H), 5.22-5.16 (m, 2H), 4.32 (d, *J* = 7.6 Hz, 1H), 2.45-2.37 (m, 1H), 2.20 (br s, 1H), 0.87 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ141.4, 140.1, 131.3, 128.6, 121.4, 117.3, 77.1, 46.4, 16.4.

HPLC: (Chiralpak AS-H/AS-H column, hexanes:*i*-PrOH = 98:2, 0.5 mL/min, 230 nm), t_{minor} = 27.9 min, t_{major} = 31.8 min; ee = 97%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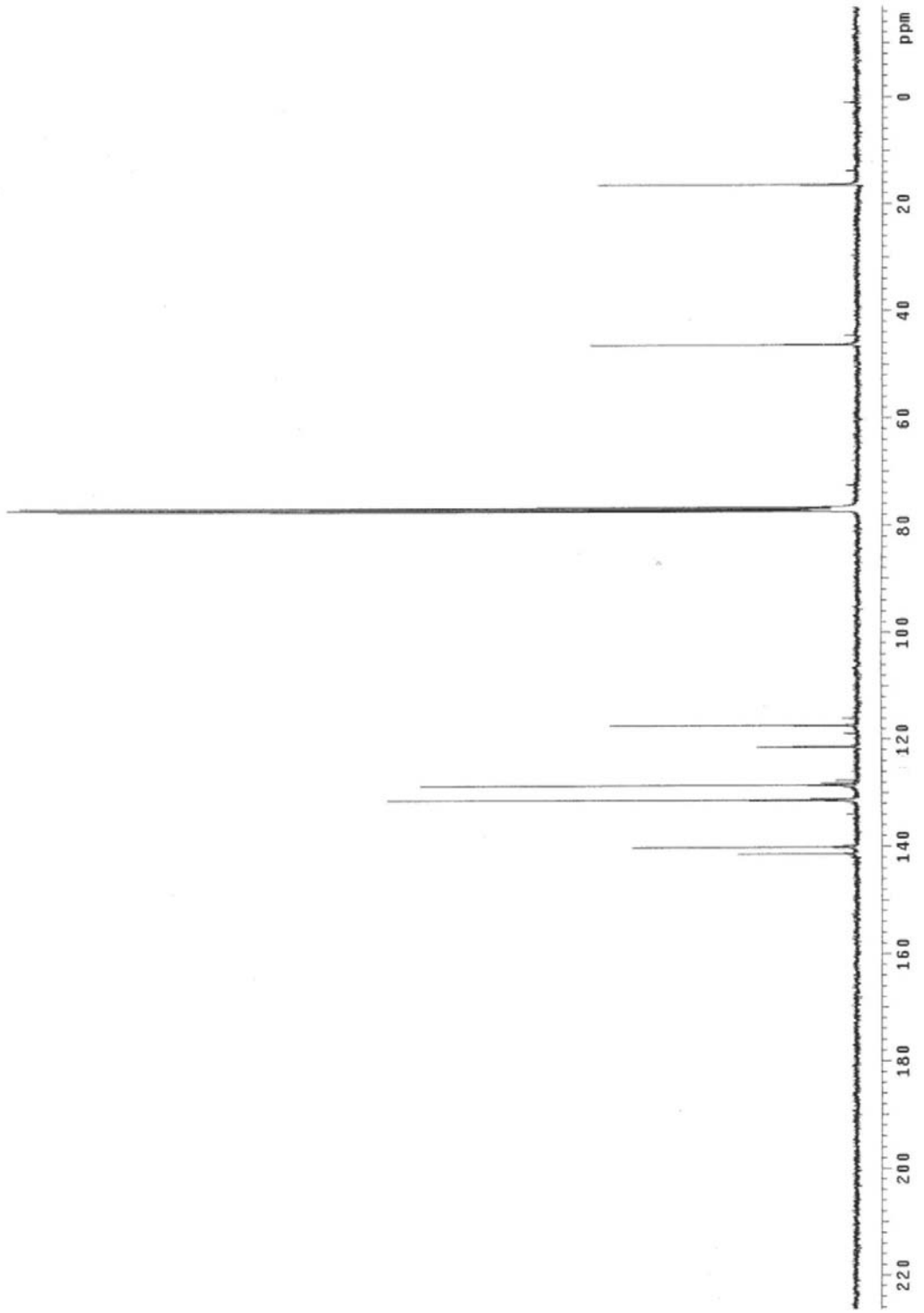
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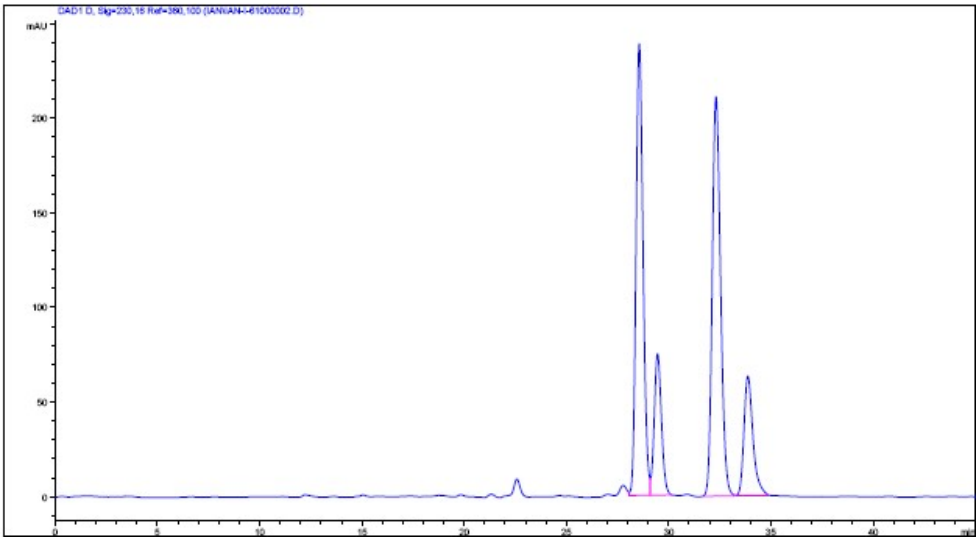
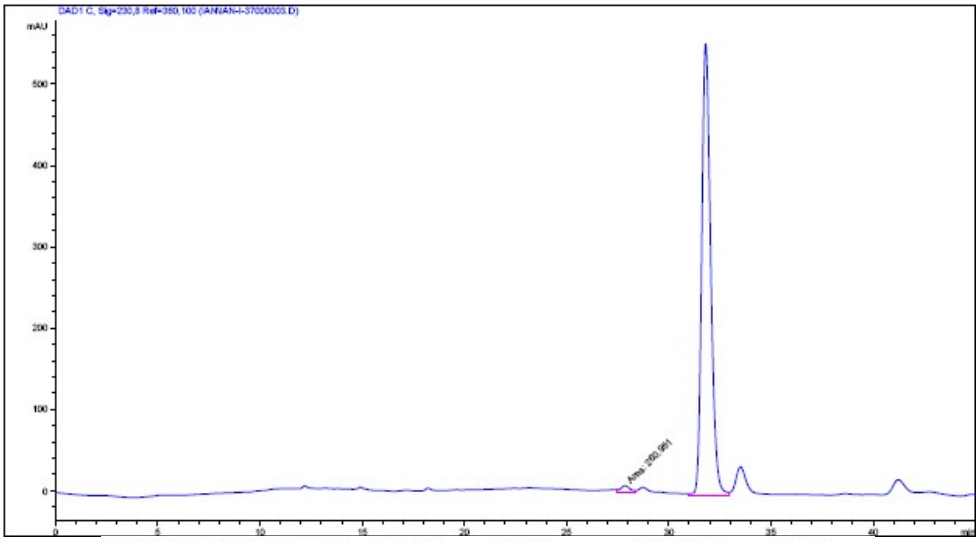
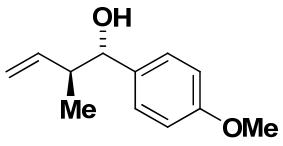


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.555	VV	0.3722	5732.60156	238.68999	48.8904
2	32.309	BB	0.4394	5992.81738	210.96976	51.1096



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.850	MM	0.5395	260.95050	8.06182	1.5010
2	31.802	VV	0.4786	1.71243e4	557.11823	98.4990

(*1S*,*2S*)-1-(4-methoxyphenyl)-2-methylbut-3-en-1-ol 4.1.4b



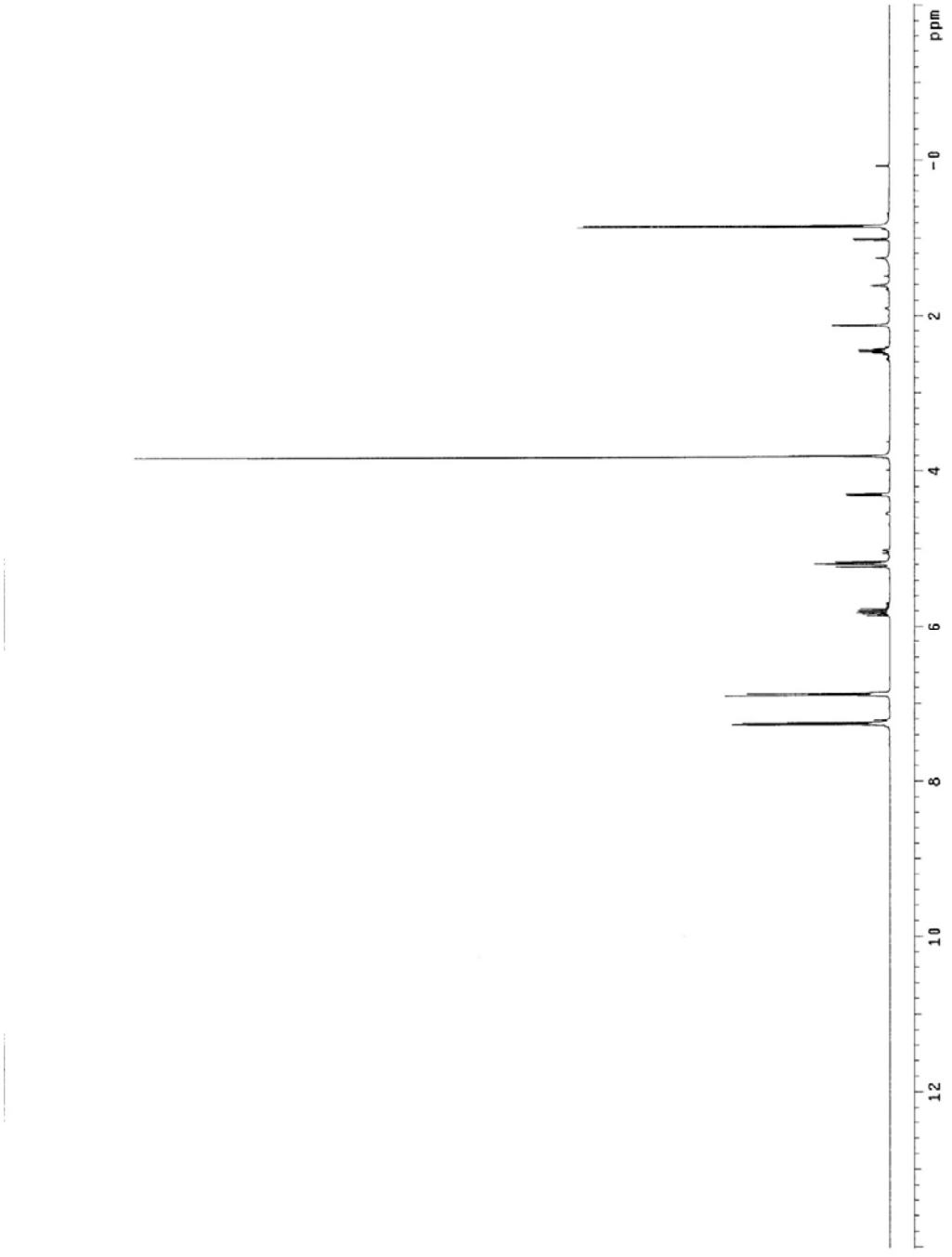
An oven-dried sealed tube under an atmosphere of N_2 was charged with (4-methoxyphenyl)methanol **4.1.2b** (27.6 mg, 0.20 mmol, 100 mol%), (*S*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (21.5 mg, 0.10 mmol, 50 mol%), THF (0.1 mL, 2.0 M), and H_2O (18 μL, 1.0 mmol, 500 mol%). But-3-en-2-yl acetate (45.6 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 60 ^oC and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **4.1.4b** (35.0 mg, 0.182 mmol) as a colorless oil in 91% yield (10:1 dr).

TLC (SiO_2): R_f = 0.4 (ethyl acetate: hexanes, 1:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 5.86-5.76 (m, 1H), 5.23-5.16 (m, 2H), 4.29 (d, *J* = 8.4 Hz, 1H), 3.80 (s, 3H), 2.48-2.42 (m, 1H), 2.15 (br s, 1H), 0.83 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ159.3, 141.2, 134.8, 128.2, 117.0, 113.9, 77.7, 55.5, 46.7, 16.8.

HPLC: (Chiralpak AD-H/AD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 230 nm), t_{minor} = 40.2 min, t_{major} = 47.6 min; ee = 95%.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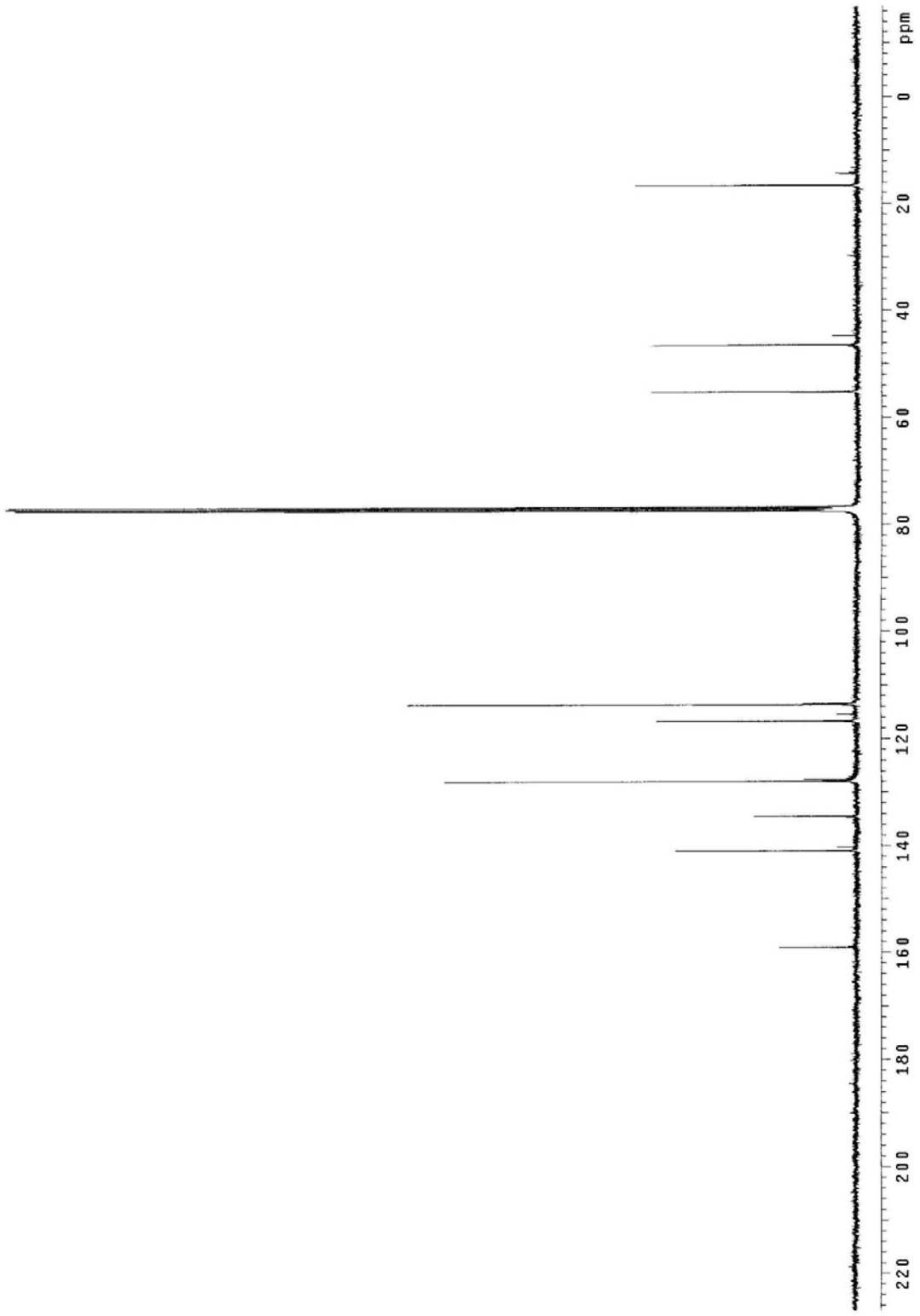
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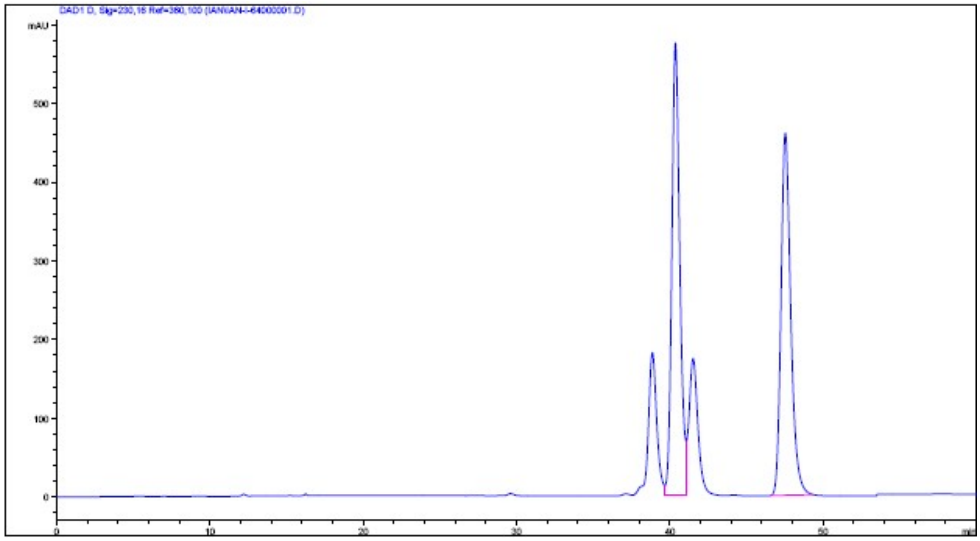

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1	40.362	VV	0.5448	2.08287e4	574.70062	50.6006
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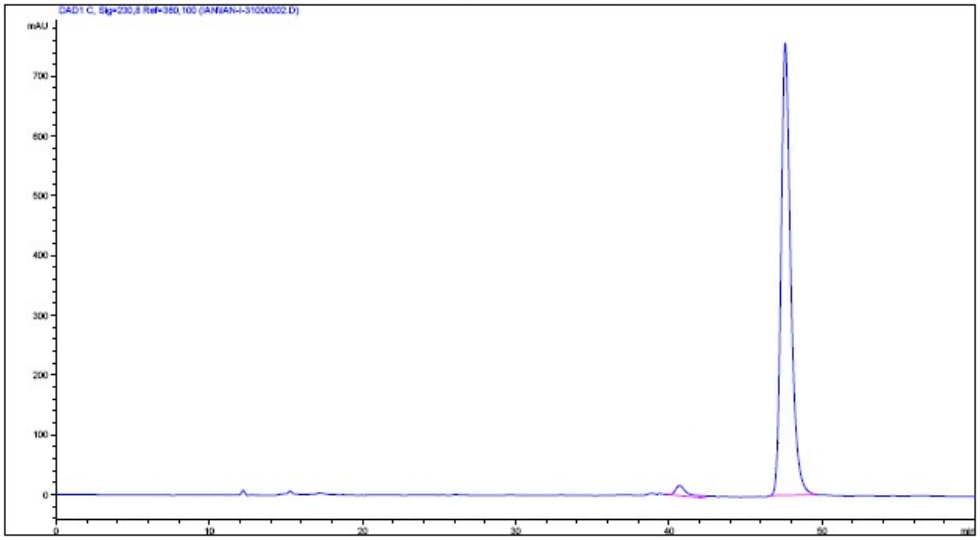

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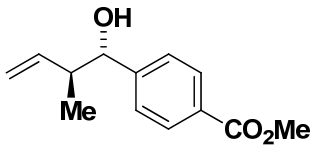
1	40.154	MM	0.9137	934.69116	17.04899	2.7209
2	47.590	BB	0.6607	3.34180e4	757.48859	97.2791

Methyl 4-((*1S*,*2S*)-1-hydroxy-2-methylbut-3-enyl)benzoate 4.1.4c



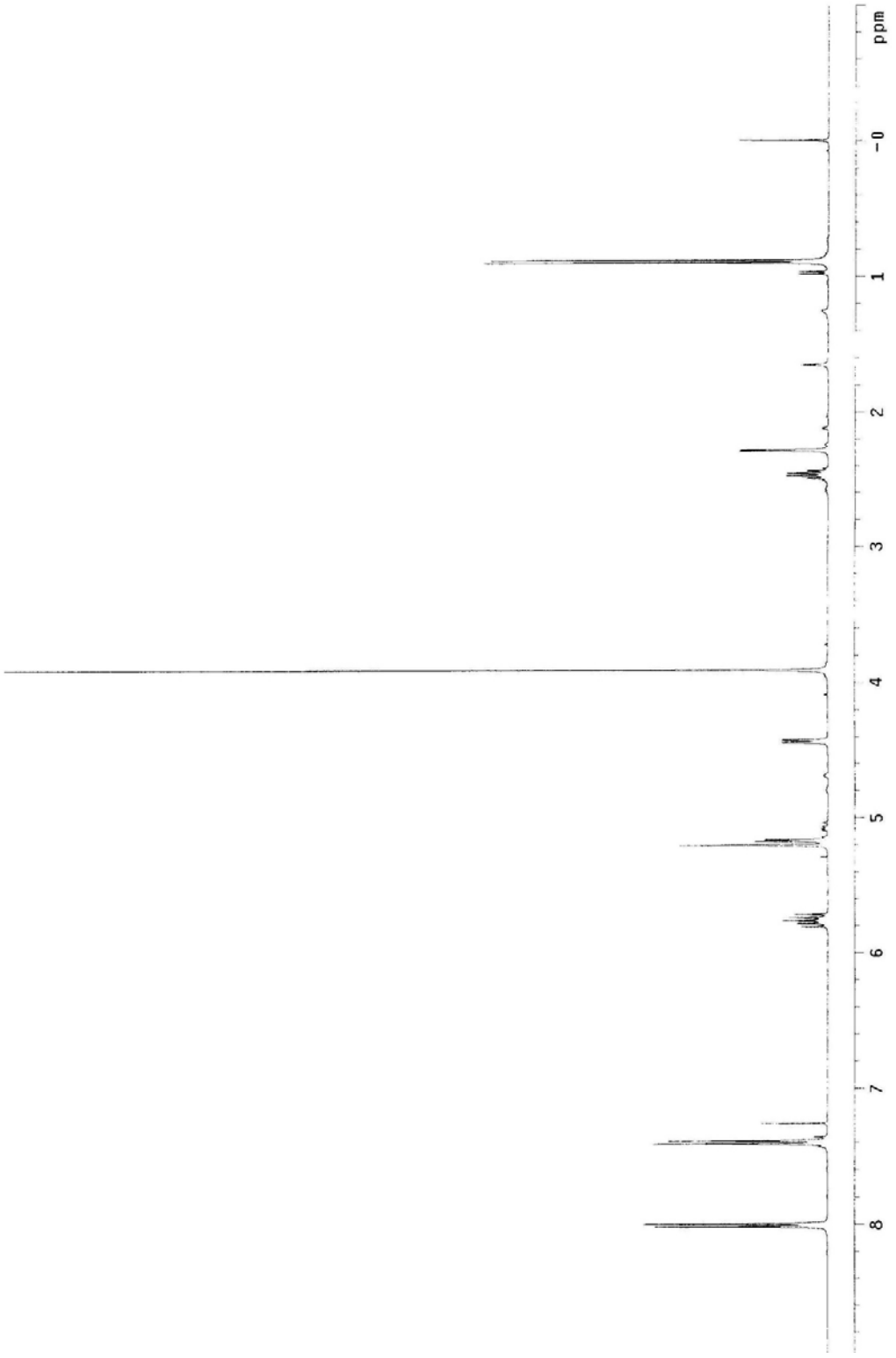
An oven-dried sealed tube under an atmosphere of N_2 was charged with methyl 4-(hydroxymethyl)benzoate **4.1.2c** (33.2 mg, 0.20 mmol, 100 mol%), (*S*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (21.5 mg, 0.10 mmol, 50 mol%), THF (0.1 mL, 2.0 M), and H_2O (18 μL, 1.0 mmol, 500 mol%). But-3-en-2-yl acetate (45.6 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 60 ^oC and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **4.1.4c** (34.4 mg, 0.156 mmol) as a colorless oil in 78% yield (11:1 dr).

TLC (SiO_2): R_f = 0.4 (ethyl acetate: hexanes, 1:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 5.79-5.69 (m, 1H), 5.17-5.12 (m, 2H), 4.40 (d, *J* = 7.2 Hz, 1H), 3.88 (s, 3H), 2.49-2.36 (m, 2H), 0.86 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ167.2, 147.9, 140.1, 129.7, 129.6, 127.0, 117.5, 77.3, 52.3, 46.5, 16.6.

HPLC: (Chiralpak AD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 254 nm), t_{minor} = 27.1 min, t_{major} = 32.3 min; ee = 98%.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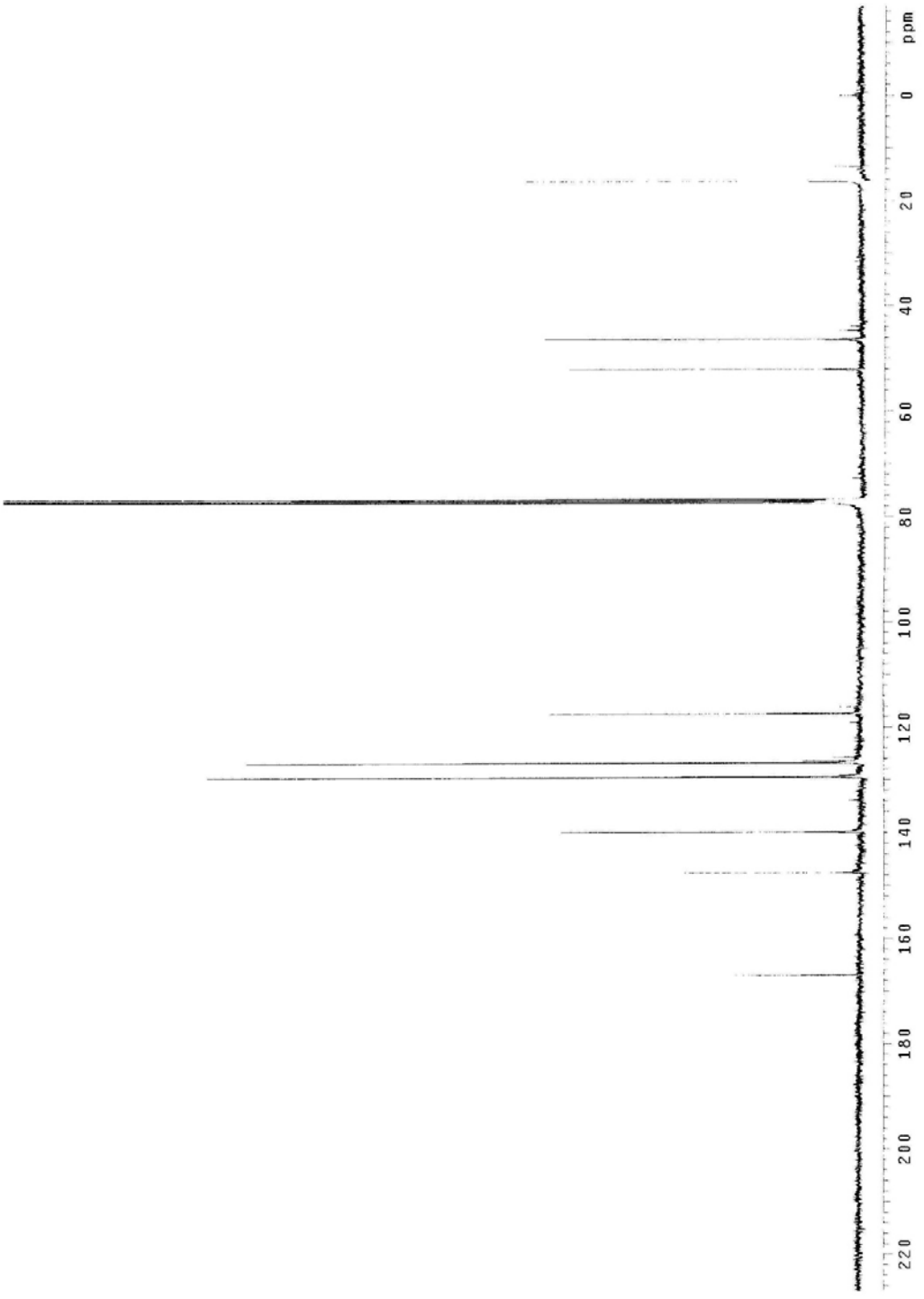
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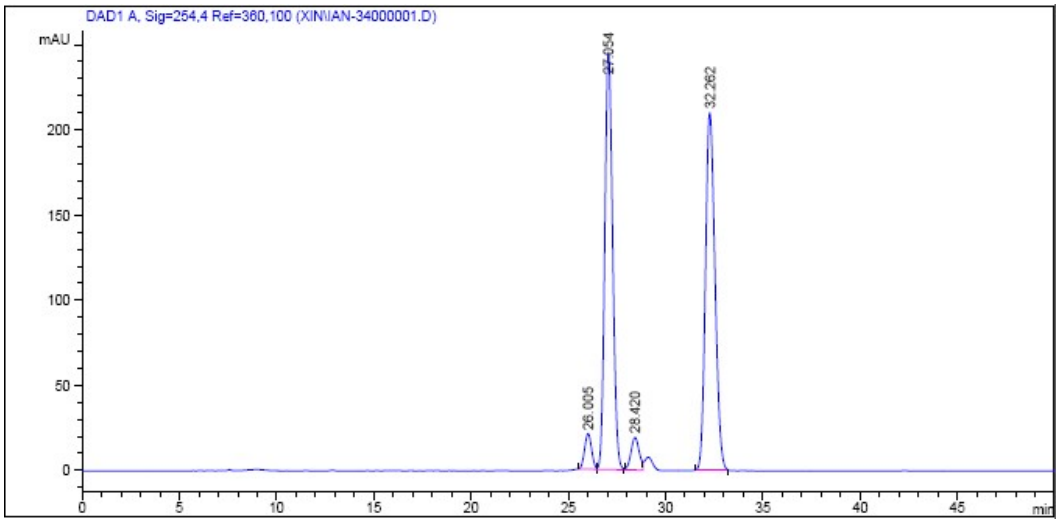
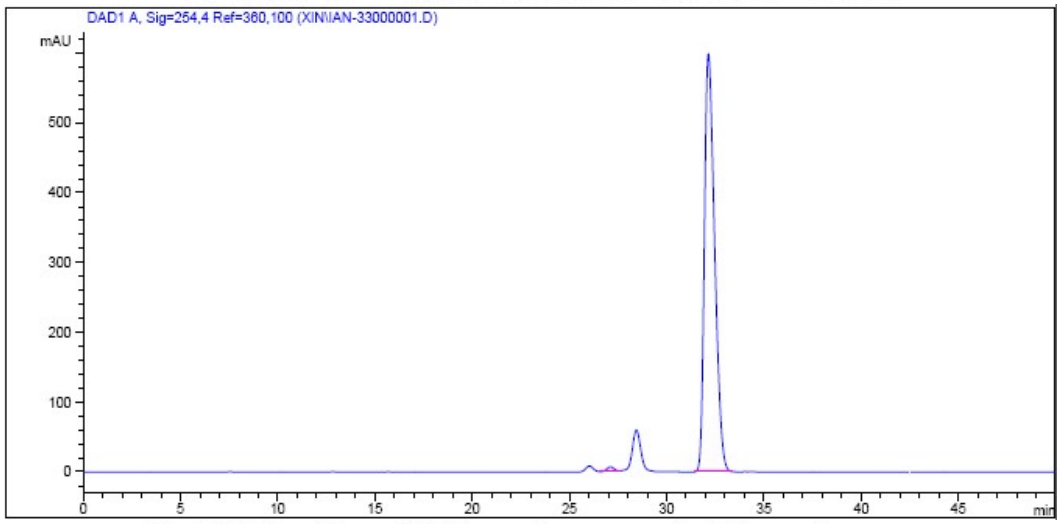
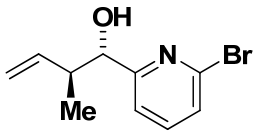


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.005	BV	0.3946	529.10156	20.95080	3.5067
2	27.054	VB	0.4368	6857.31104	244.83498	45.4484
3	28.420	BV	0.4493	565.99902	19.12413	3.7513
4	32.262	BB	0.5267	7135.71631	209.86855	47.2936



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.101	VV	0.4236	193.71434	6.98357	0.8779
2	32.133	BB	0.5662	2.18716e4	598.67102	99.1221

(*1S*,*2S*)-1-(6-bromopyridin-2-yl)-2-methylbut-3-en-1-ol 4.1.4d



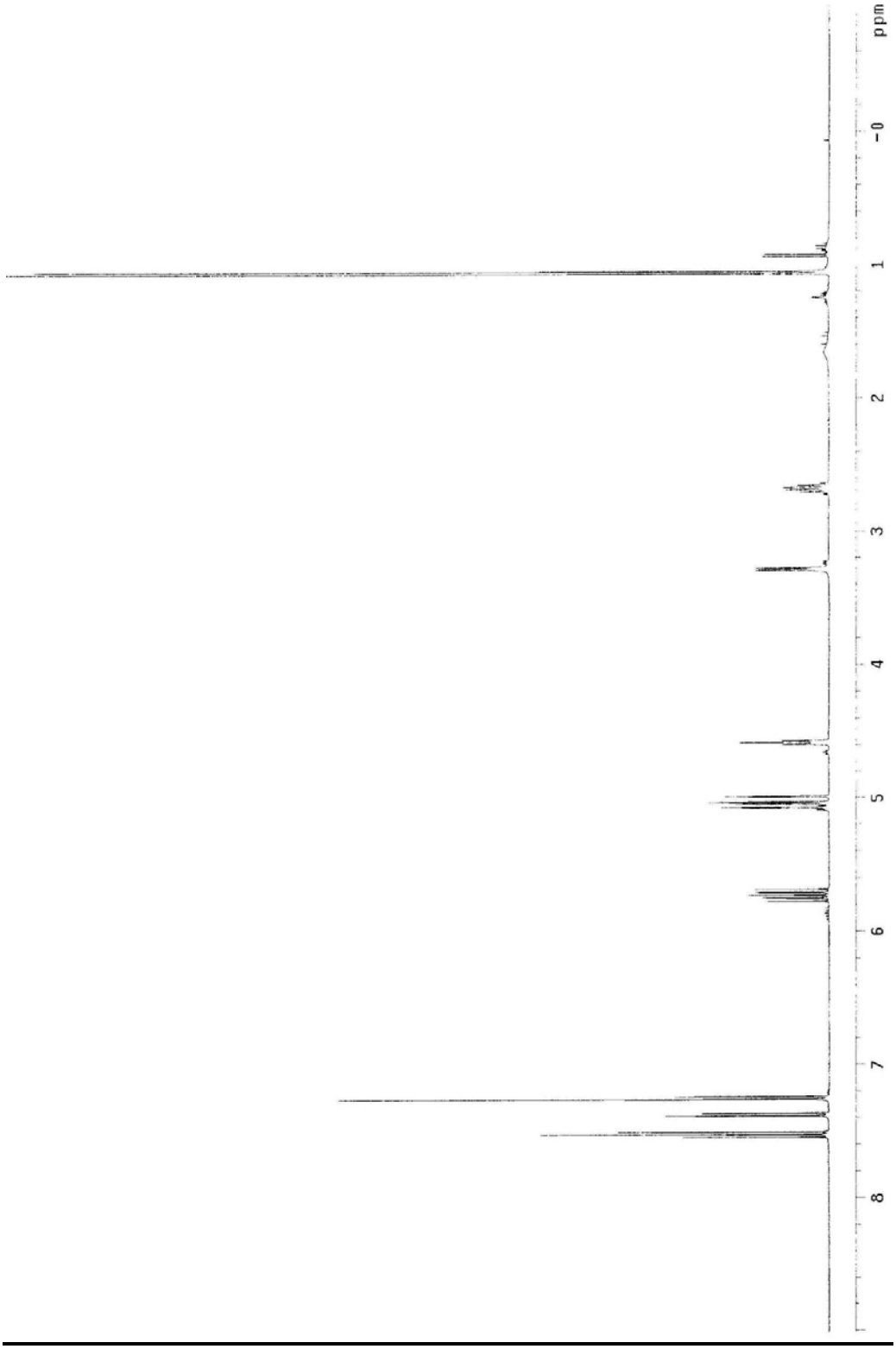
An oven-dried sealed tube under an atmosphere of N_2 was charged with (6-bromopyridin-2-yl)methanol **4.1.2d** (37.6 mg, 0.20 mmol, 100 mol%), (*S*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (21.5 mg, 0.10 mmol, 50 mol%), THF (0.1 mL, 2.0 M), and H_2O (18 μL, 1.0 mmol, 500 mol%). But-3-en-2-yl acetate (45.6 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 60 ^oC and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **4.1.4d** (24.2 mg, 0.100 mmol) as a colorless oil in 50% yield (14:1 dr).

TLC (SiO_2): R_f = 0.3 (ethyl acetate: hexanes, 1:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 5.73 (dt, *J* = 17.2, 10.4, 1H), 5.10-4.99 (m, 2H), 4.58 (t, *J* = 5.2 Hz, 1H), 3.28 (d, *J* = 6.0 Hz, 1H), 2.72-2.64 (m, 1H), 1.06 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 141.0, 138.7, 138.6, 126.7, 120.0, 116.5, 44.6, 16.1.

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 210 nm), t_{major} = 12.1 min, t_{minor} = 16.8 min ; ee = 98%.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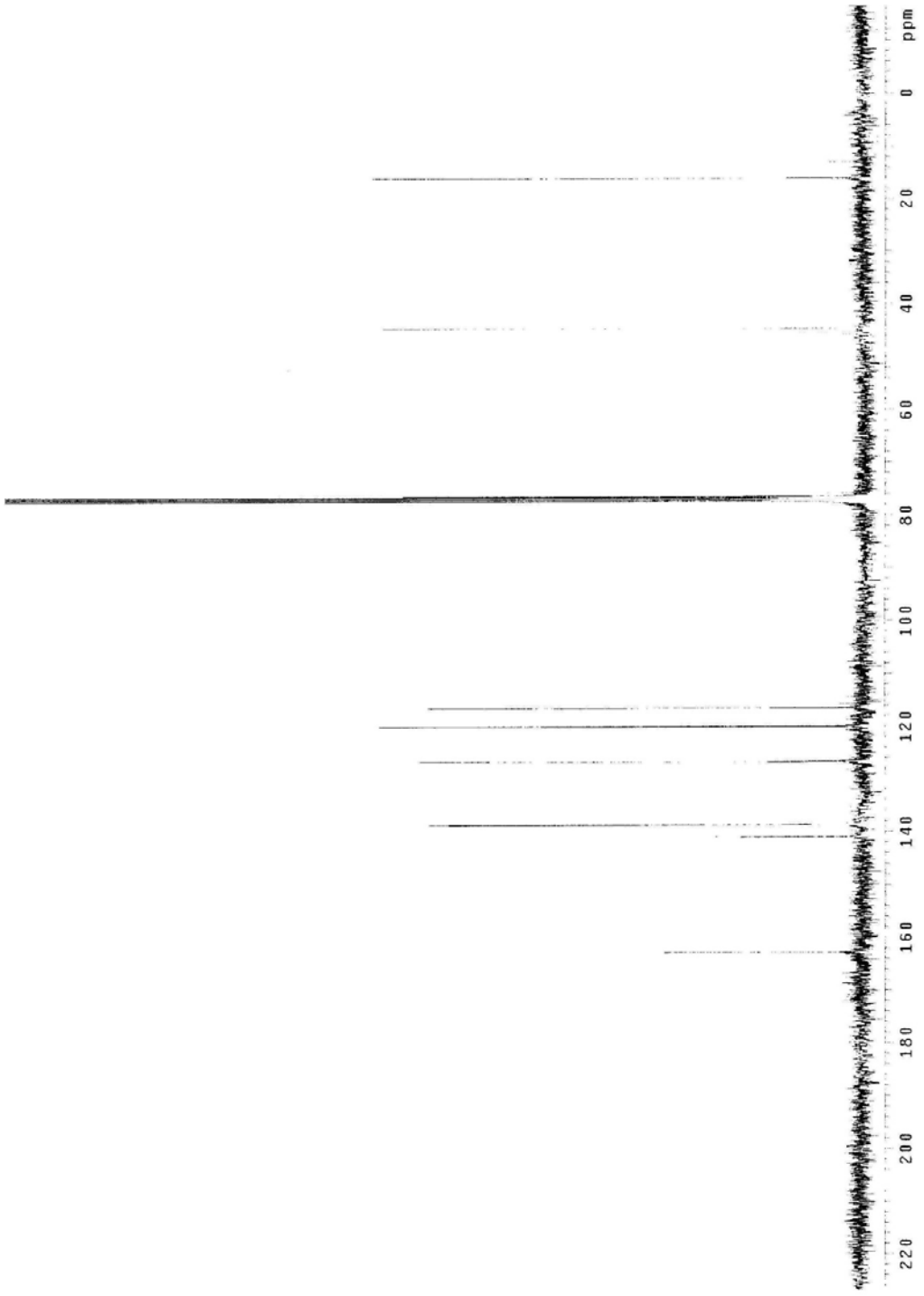
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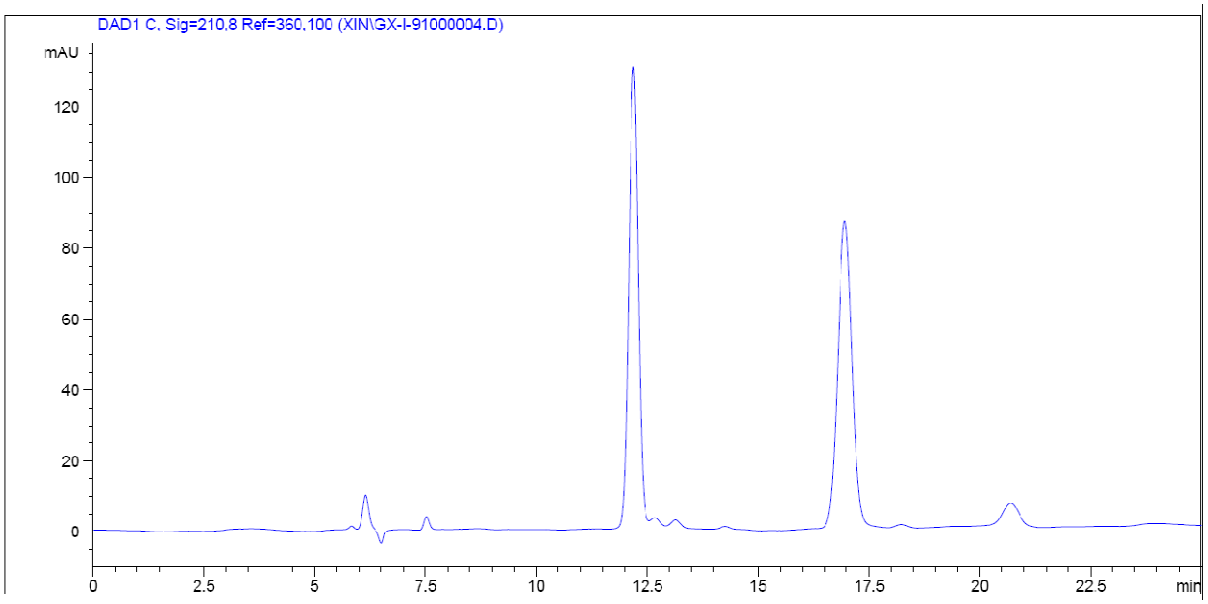

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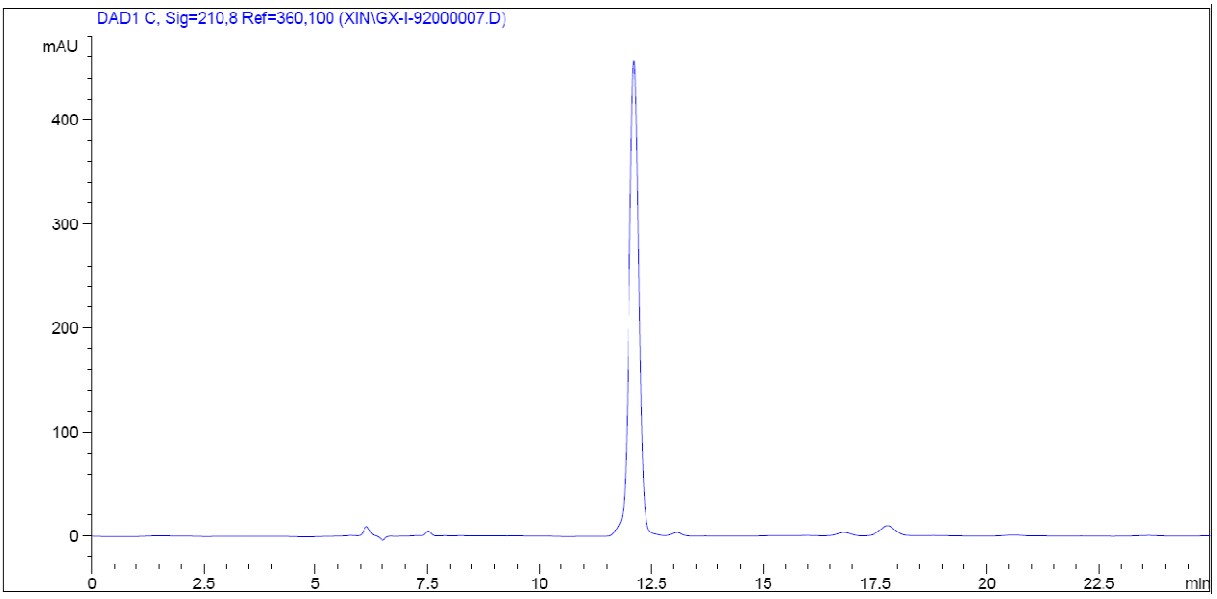
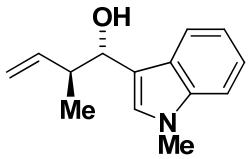


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.112	BB	0.2351	6938.44824	456.97983	99.1868
2	16.806	BB	0.2874	56.88535	2.89344	0.8132

(*1S*,*2S*)-2-methyl-1-(1-methyl-1*H*-indol-3-yl)but-3-en-1-ol 4.1.4e



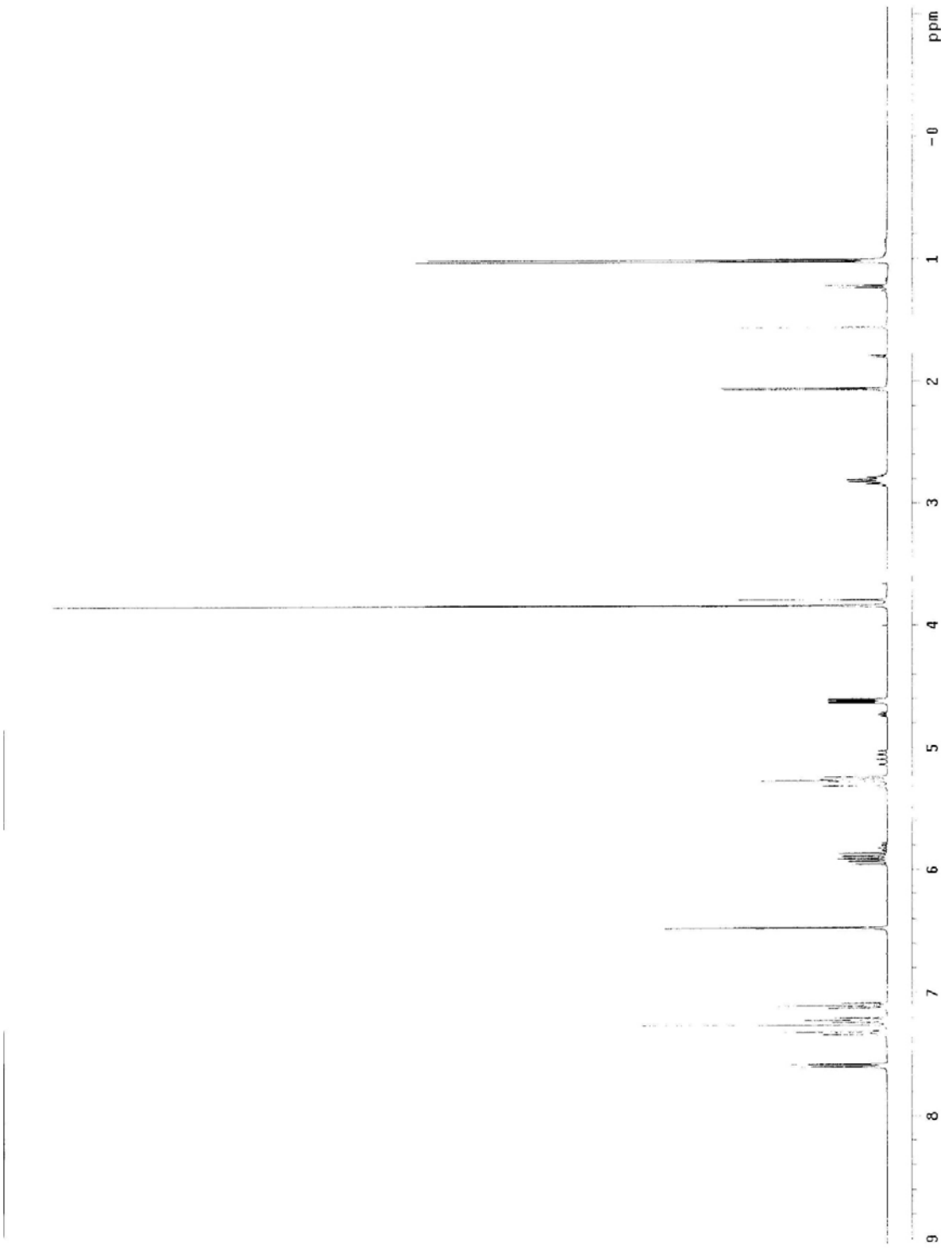
An oven-dried sealed tube under an atmosphere of N_2 was charged with (1-methyl-1*H*-indol-3-yl)methanol **4.1.2e** (32.2 mg, 0.20 mmol, 100 mol%), (*S*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (21.5 mg, 0.10 mmol, 50 mol%), THF (0.1 mL, 2.0 M), and H_2O (18 μL, 1.0 mmol, 500 mol%). But-3-en-2-yl acetate (45.6 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 60 ^oC and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **4.1.4e** (32.3 mg, 0.150 mmol) as a colorless oil in 75% yield (7:1 dr).

TLC (SiO_2): R_f = 0.4 (ethyl acetate: hexanes, 1:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 6.48 (s, 1H), 5.98-5.88 (m, 1H), 5.33-5.25 (m, 2H), 4.60 (d, *J* = 8.4 Hz, 1H), 3.81 (s, 3H), 2.86-2.78 (m, 1H), 2.22 (br s, 1H), 1.03 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7, 140.3, 138.2, 127.5, 121.9, 120.9, 119.8, 117.4, 109.4, 100.8, 71.4, 44.3, 30.7, 17.5.

HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 93:7, 0.5 mL/min, 254 nm), t_{major} = 53.3 min, t_{minor} = 66.0 min; ee = 98%.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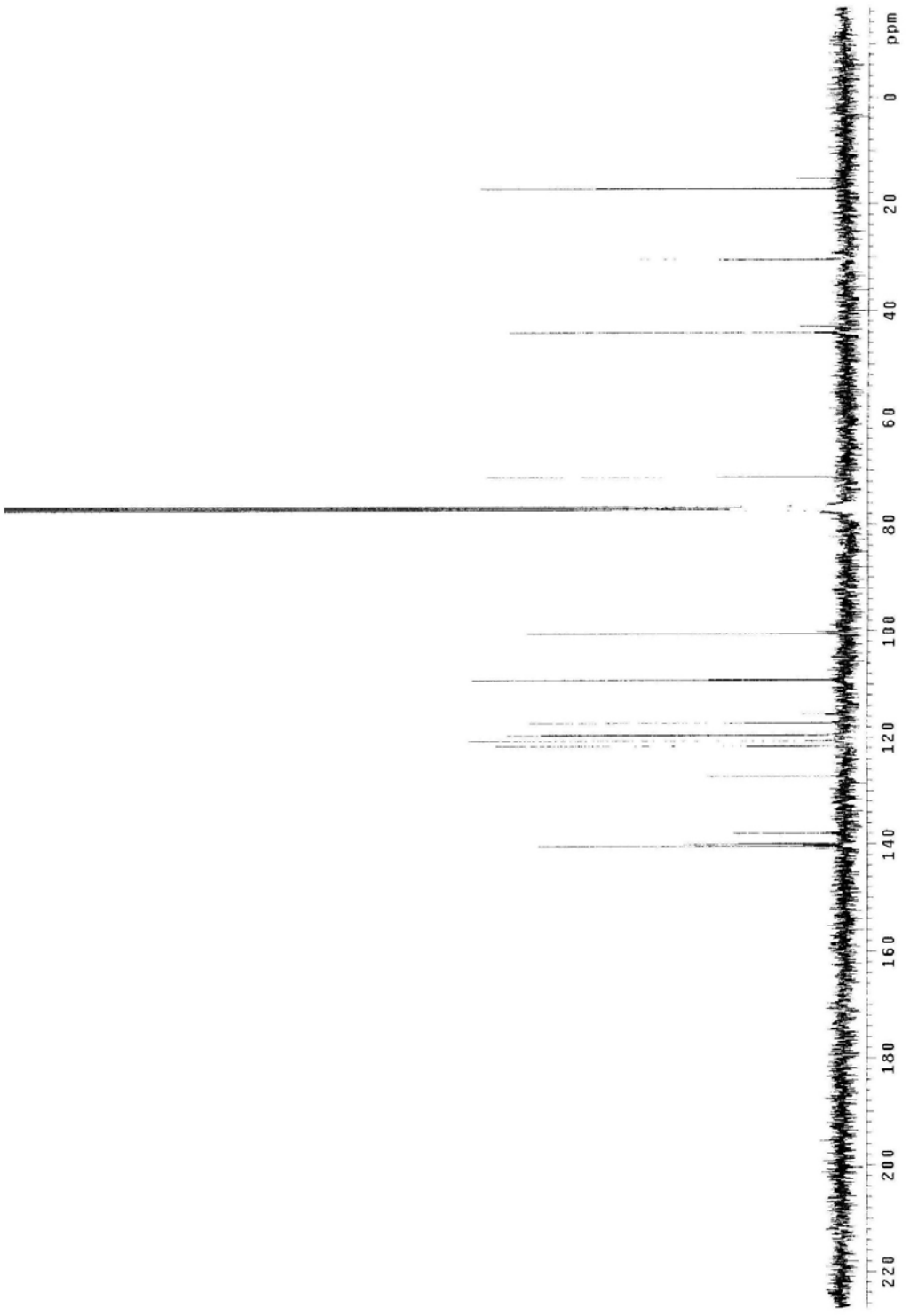
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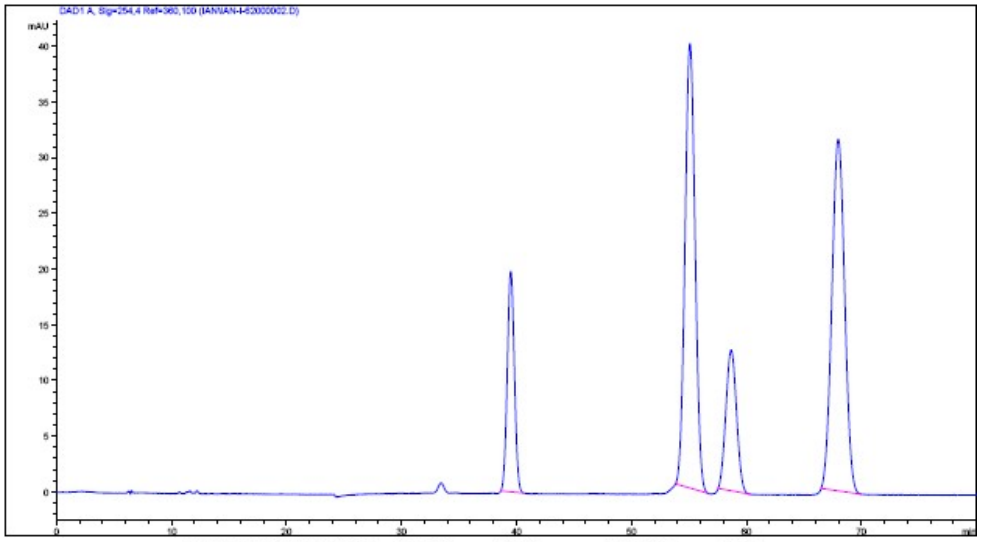
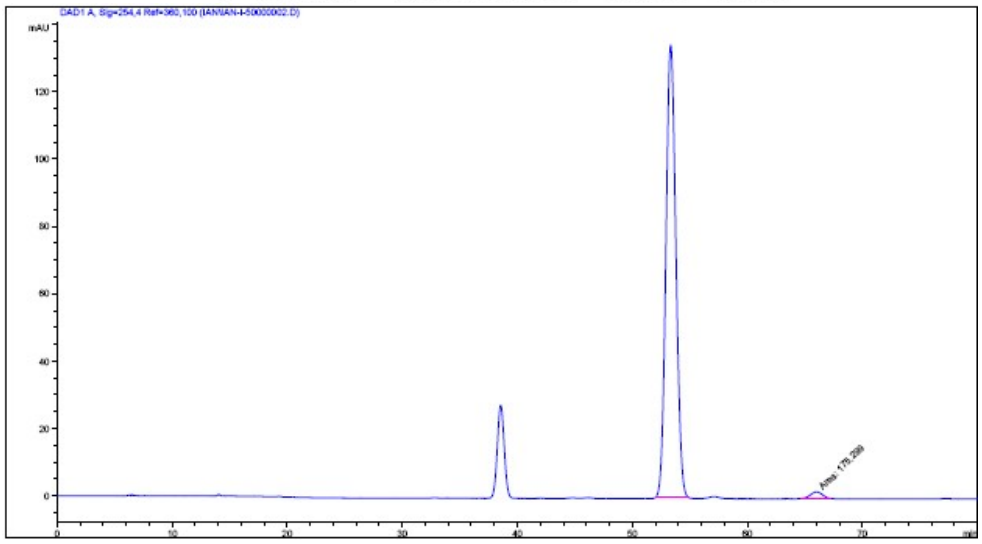


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	39.492	BB	0.6589	850.65906	19.81396	13.0118
2	55.079	BB	0.9157	2436.11816	39.93385	37.2632
3	58.665	BB	0.8004	813.51562	12.64772	12.4437
4	67.979	BB	1.0884	2437.29663	31.58078	37.2813



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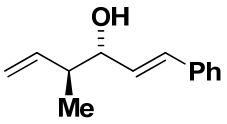
1	53.326	BB	0.9330	8082.24170	134.51173	98.8771
2	66.037	MM	1.3160	175.29871	2.22011	1.1229

(*3R*,*4S*,*E*)-4-methyl-1-phenylhexa-1,5-dien-3-ol 4.1.4f



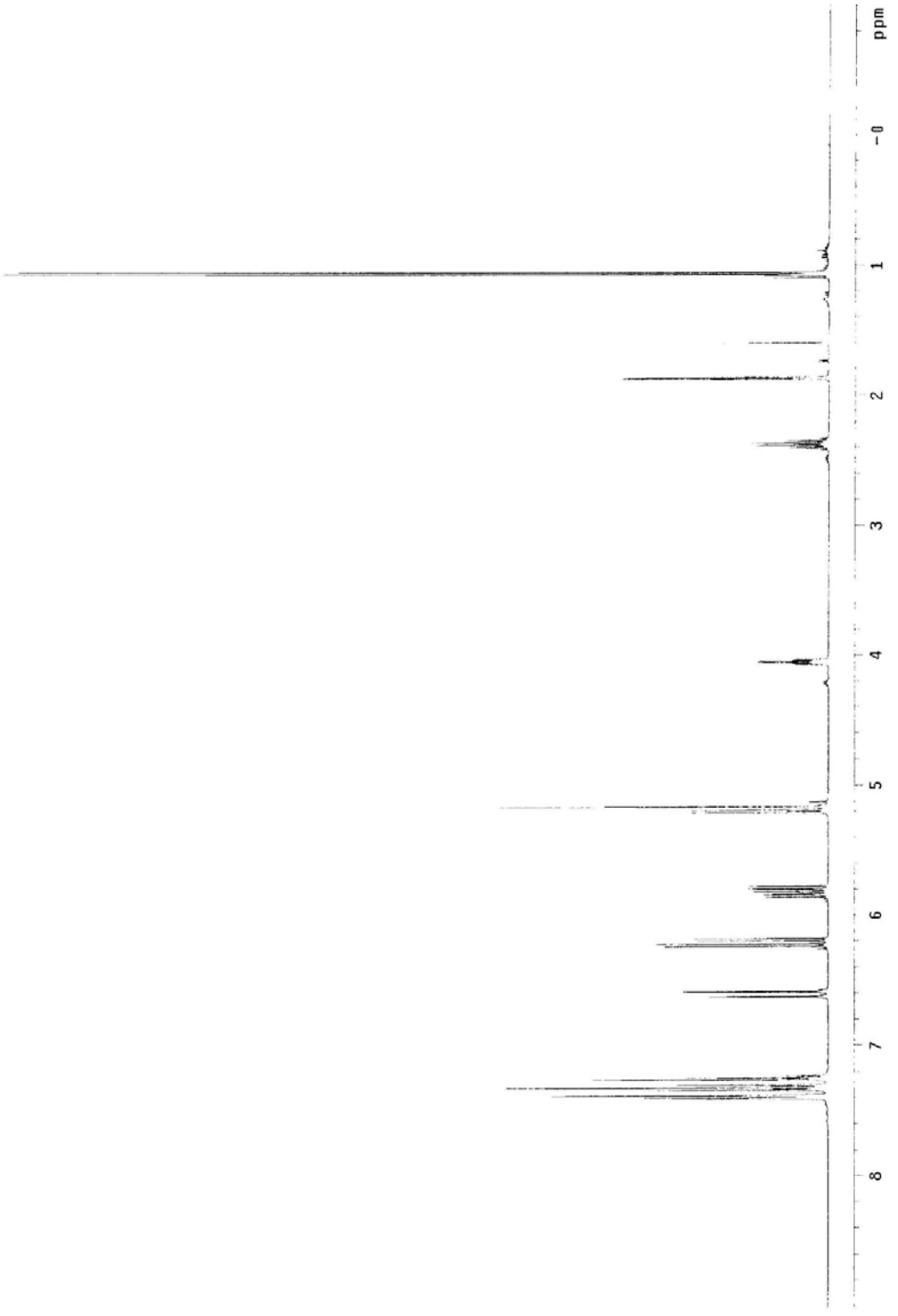
An oven-dried sealed tube under an atmosphere of N_2 was charged with *trans*-cinnamyl alcohol **4.1.2f** (26.8 mg, 0.20 mmol, 100 mol%), (*S*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (21.5 mg, 0.10 mmol, 50 mol%), THF (0.1 mL, 2.0 M), and H_2O (18 μL, 1.0 mmol, 500 mol%). But-3-en-2-yl acetate (45.6 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **4.1.4f** (27.1 mg, 0.144 mmol) as a colorless oil in 72% yield (10:1 dr).

TLC (SiO_2): R_f = 0.3 (ethyl acetate:hexanes, 1:10).

^{1}H NMR (400 MHz, CDCl3): δ 7.41-7.23 (m, 5H), 6.61 (d, *J* = 16.0 Hz, 1H), 6.21 (dd, *J* = 16.0, 7.2 Hz, 1H), 5.88-5.78 (m, 1H), 5.21-5.16 (m, 2H), 4.06 (t, *J* = 6.8 Hz, 1H), 2.41-2.35 (m, 1H), 1.99 (br s, 1H), 1.06 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl3): δ 140.4, 136.9, 132.0, 130.4, 128.8, 127.9, 126.8, 117.0, 76.4, 44.9, 16.3.

HPLC: (Chiralpak AS-H/AS-H column, hexanes:*i*-PrOH = 98:2, 0.5 mL/min, 254 nm), t_{minor} = 26.8 min, t_{major} = 31.5 min; ee = 93%.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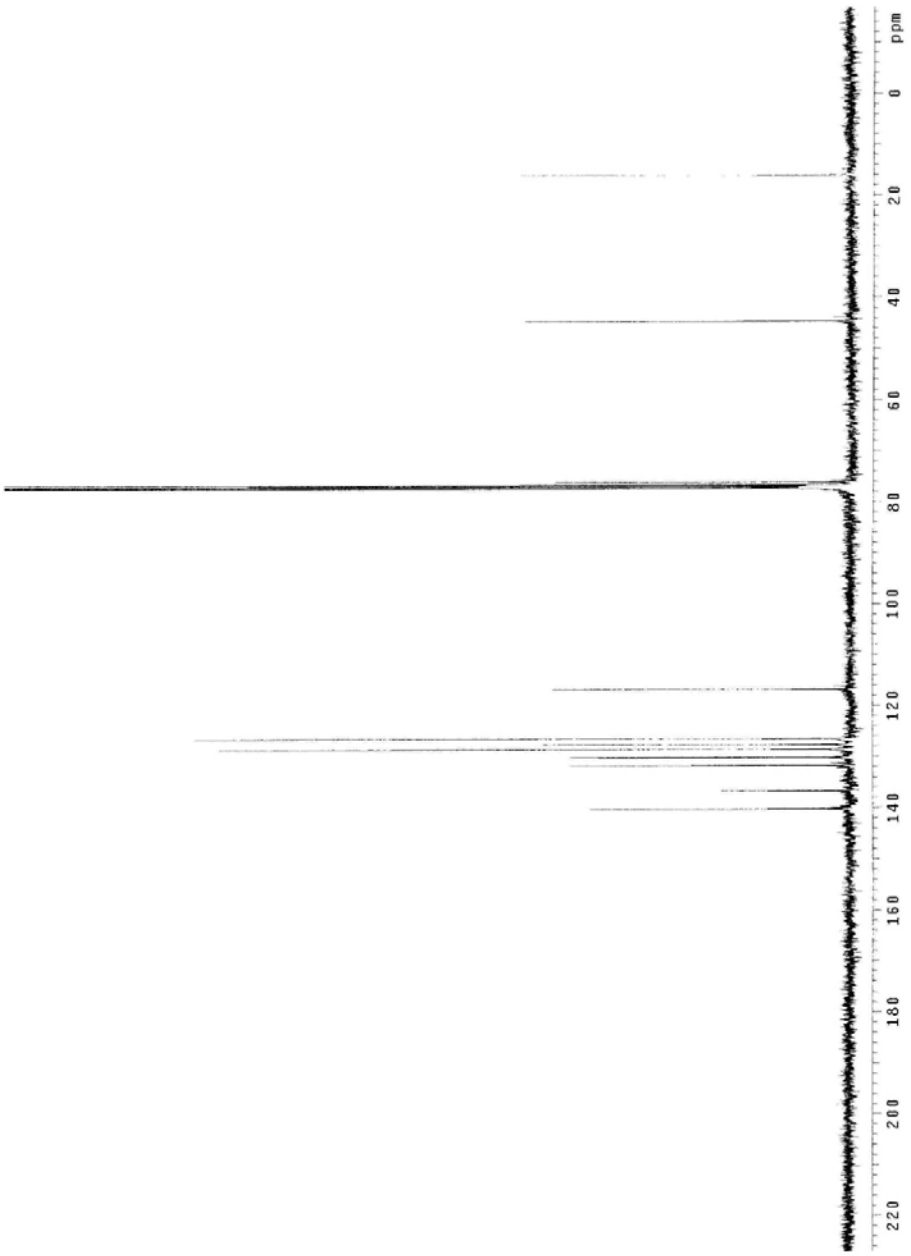
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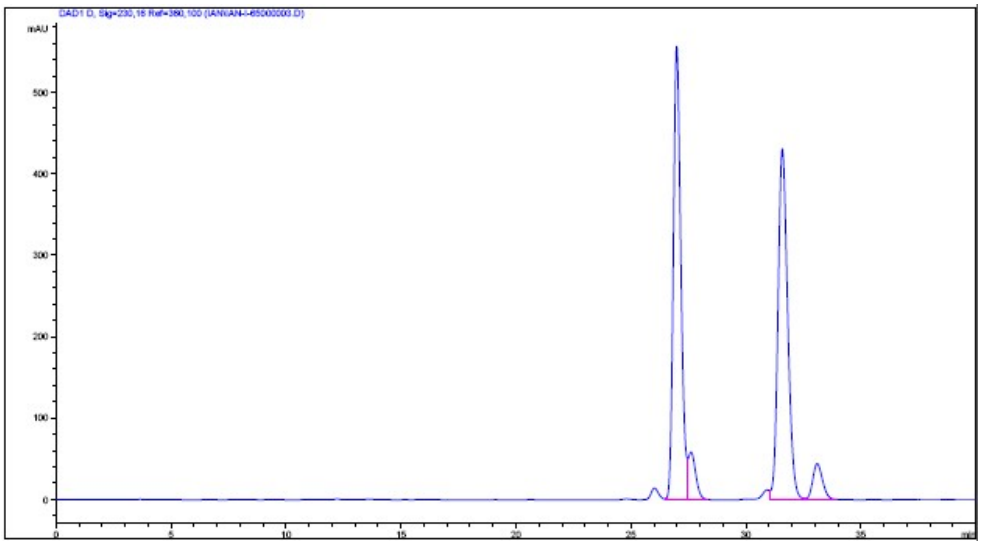

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.987	VV	0.3475	1.26759e4	557.10522	45.5873
2	27.611	VB	0.3413	1330.46252	58.51318	4.7848
3	31.580	VB	0.4475	1.25149e4	430.09030	45.0083
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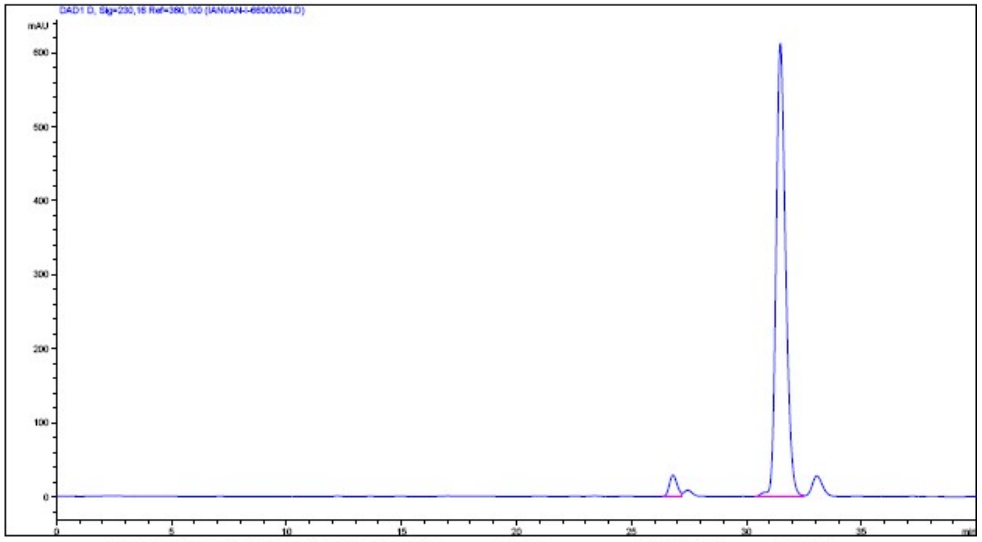
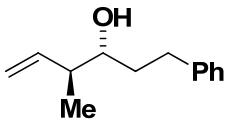


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.797	BV	0.3670	682.55109	28.95984	3.7180
2	31.467	BB	0.4385	1.76757e4	612.88232	96.2820

(*3R*,*4S*)-4-methyl-1-phenylhex-5-en-3-ol 4.1.4g



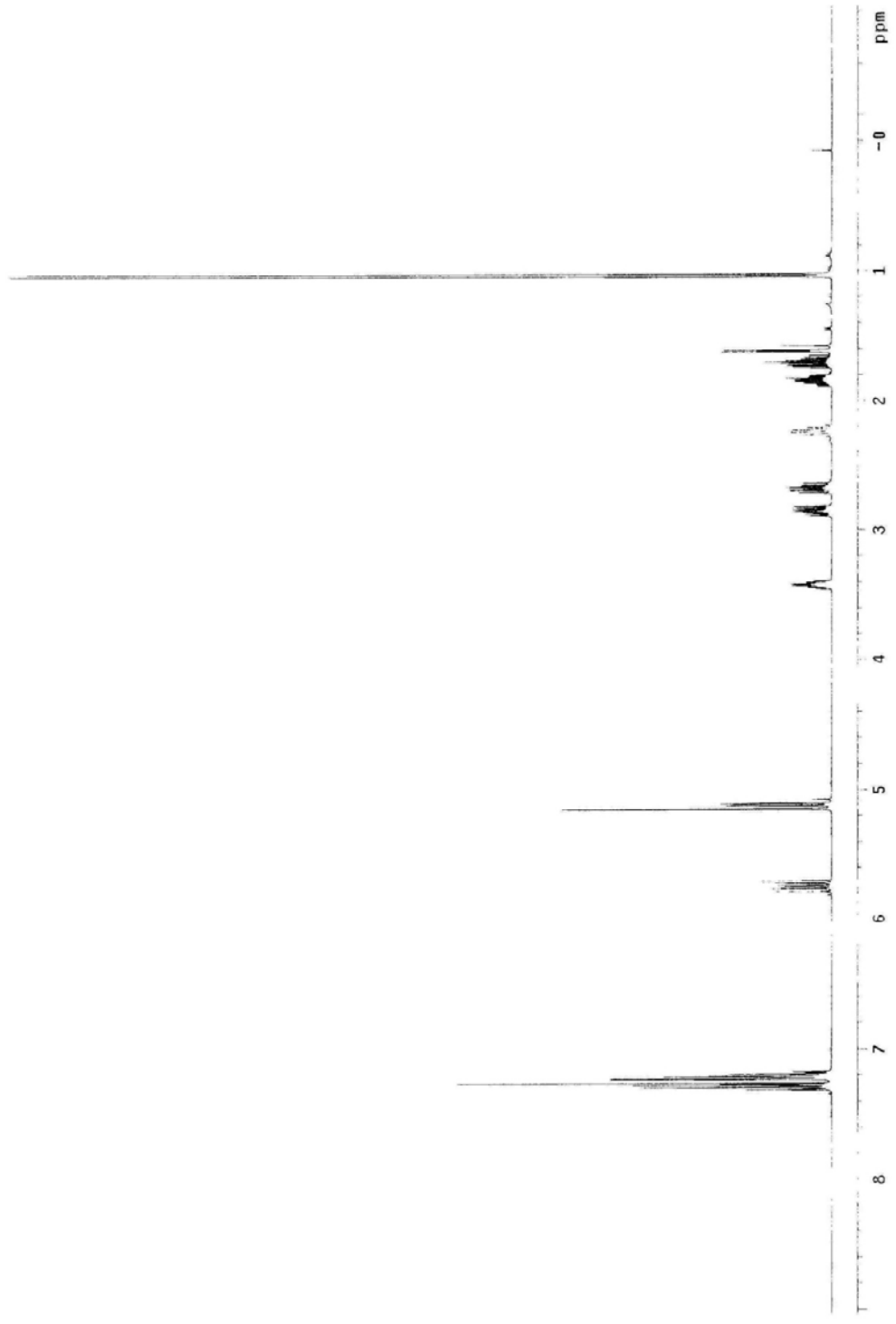
An oven-dried sealed tube under an atmosphere of N_2 was charged with 3-phenylpropan-1-ol **4.1.2g** (27.2 mg, 0.20 mmol, 100 mol%), (*S*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (21.5 mg, 0.10 mmol, 50 mol%), THF (0.1 mL, 2.0 M), and H_2O (18 μL, 1.0 mmol, 500 mol%). But-3-en-2-yl acetate (45.6 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 60 ^oC and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **4.1.4g** (27.0 mg, 0.142 mmol) as a colorless oil in 71% yield (>20:1 dr).

TLC (SiO_2): R_f = 0.4 (ethyl acetate: hexanes, 1:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.17 (m, 5H), 5.80-5.70 (m, 1H), 5.15-5.10 (m, 2H), 3.43-3.40 (m, 1H), 2.89-2.81 (m, 1H), 2.72-2.64 (m, 1H), 2.26-2.20 (m, 1H), 1.89-1.80 (m, 1H), 1.75-1.62 (m, 2H), 1.03 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.6, 140.4, 128.7, 128.6, 126.0, 116.8, 74.2, 44.6, 36.4, 32.4, 16.5.

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 97:3, 0.7 mL/min, 254 nm), t_{minor} = 11.5 min, t_{major} = 18.7 min; ee = 99%.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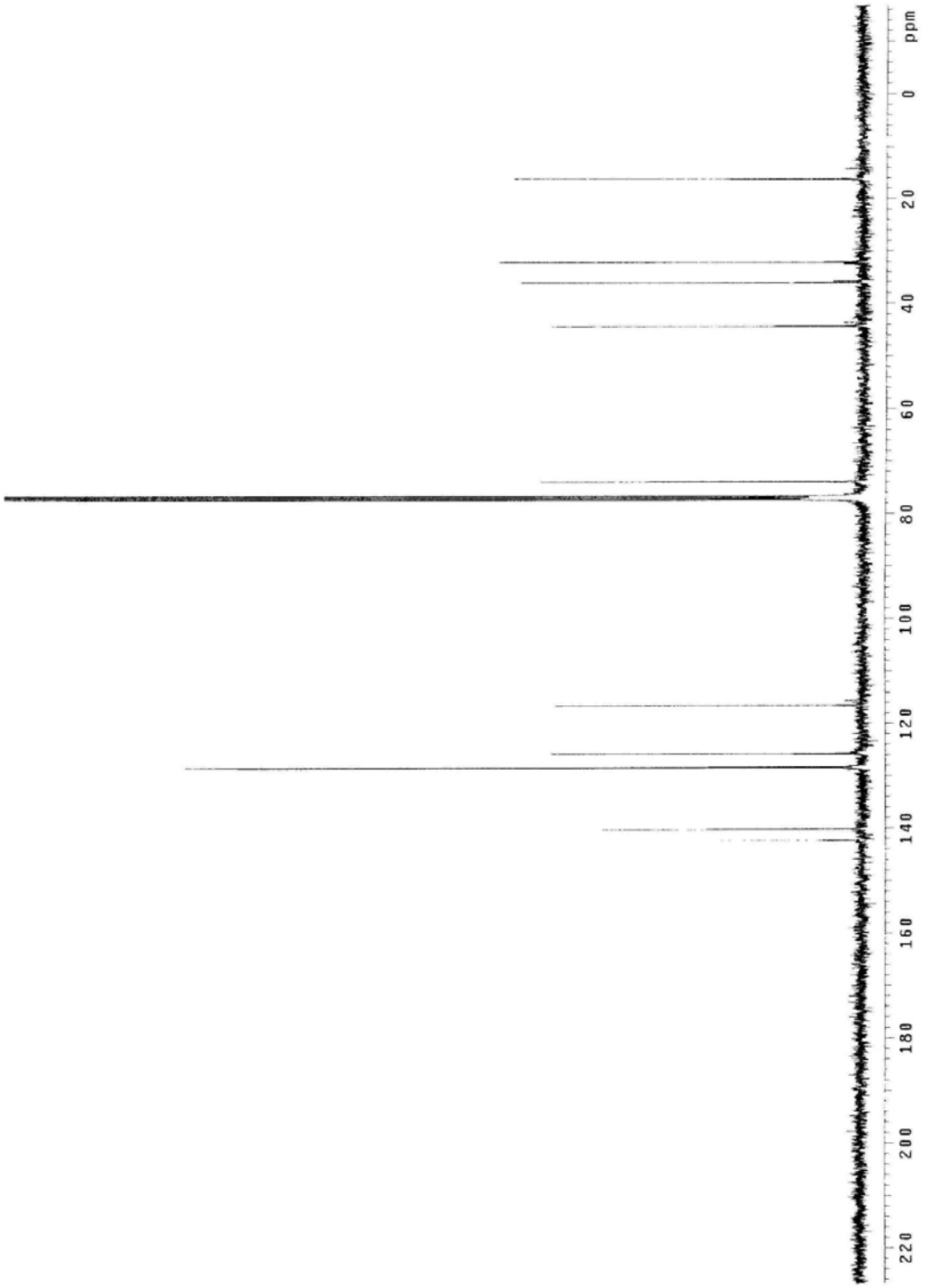
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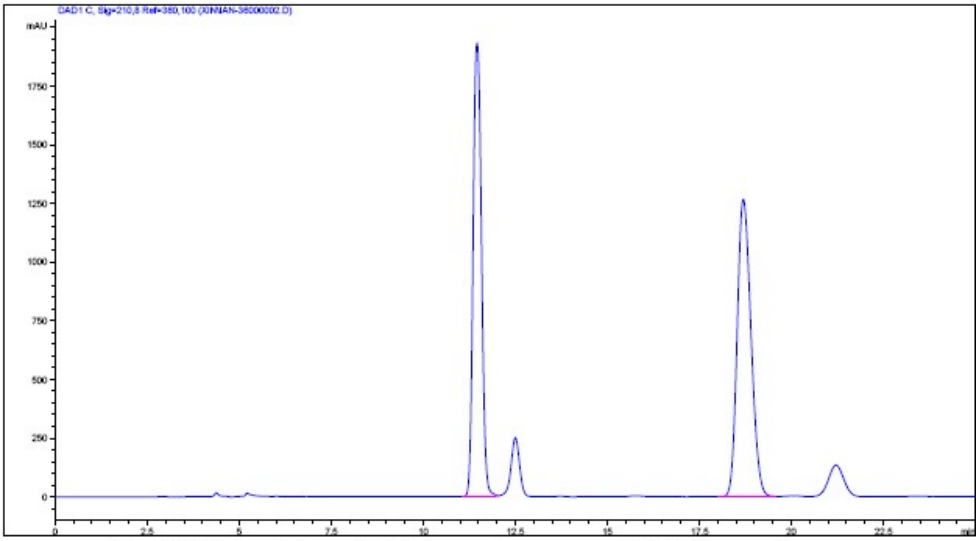
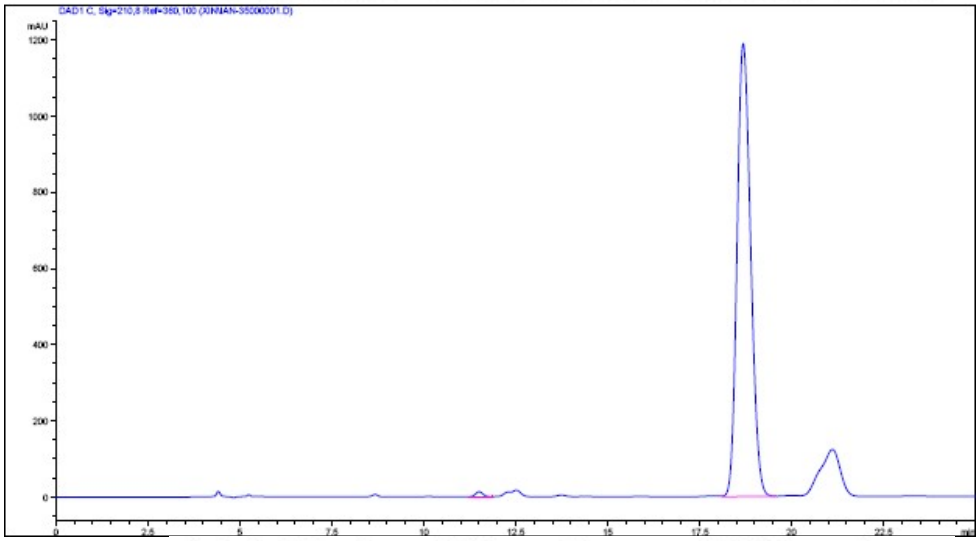
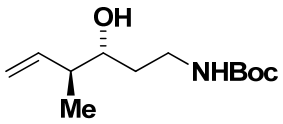


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.459	BV	0.2517	3.04228e4	1932.34814	47.9834
2	18.694	VB	0.4076	3.29800e4	1267.50708	52.0166



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.503	BB	0.2170	179.06799	12.97591	0.5821
2	18.685	BB	0.4019	3.05811e4	1189.62244	99.4179

***tert*-butyl (*3R,4S*)-3-hydroxy-4-methylhex-5-enylcarbamate 4.1.4h**



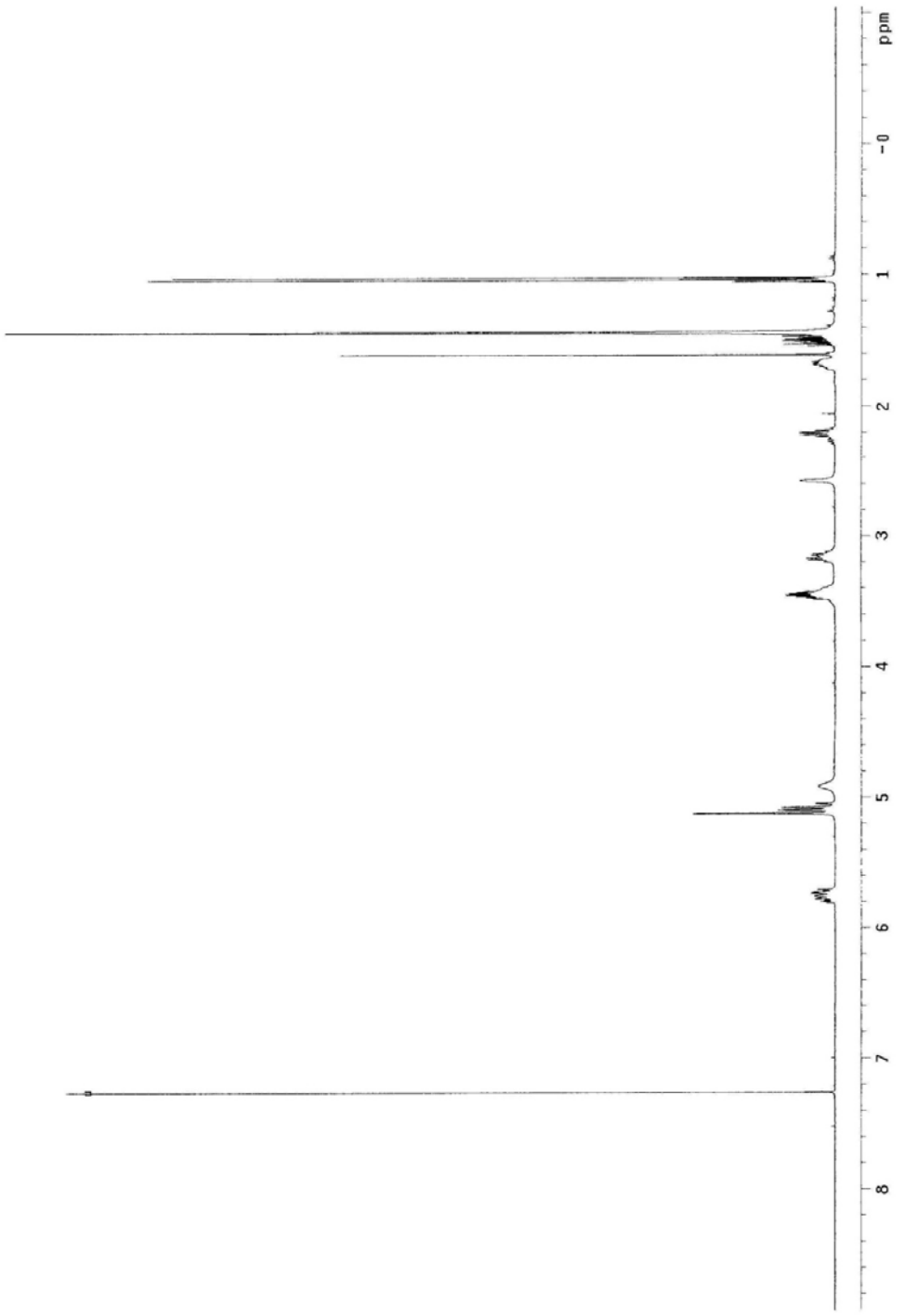
An oven-dried sealed tube under an atmosphere of N_2 was charged with *tert*-butyl 3-hydroxypropylcarbamate **4.1.2h** (35.0 mg, 0.20 mmol, 100 mol%), (*S*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (21.5 mg, 0.10 mmol, 50 mol%), THF (0.1 mL, 2.0 M), and H_2O (18 μL, 1.0 mmol, 500 mol%). But-3-en-2-yl acetate (45.6 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **4.1.4h** (32.6 mg, 0.142 mmol) as a colorless oil in 71% yield (>20:1 dr).

TLC (SiO_2): R_f = 0.5 (ethyl acetate:hexanes, 1:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 (dtd, *J* = 17.2, 10.0, 0.4 Hz, 1H), 5.12-5.05 (m, 2H), 4.91 (br, 1H), 3.48-3.41 (m, 2H), 3.20-3.11 (m, 1H), 2.58 (d, *J* = 2.8 Hz, 1H), 2.30-2.17 (m, 1H), 1.72-1.64 (m, 1H), 1.54-1.45 (m, 1H), 1.44 (s, 9H), 1.03 (d, *J* = 6.8 Hz,3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 140.4, 116.1, 79.3, 72.6, 44.2, 37.7, 34.2, 28.4, 16.2.

HPLC: Enantiomeric excess was determined by HPLC analysis of the 4-nitrobenzoate derivative of the product (Chiralcel OJ-H column, hexanes:*i*-PrOH = 98:2, 0.75 mL/min, 254 nm), t_{minor} = 24.4 min, t_{major} = 28.1 min; ee = 96%.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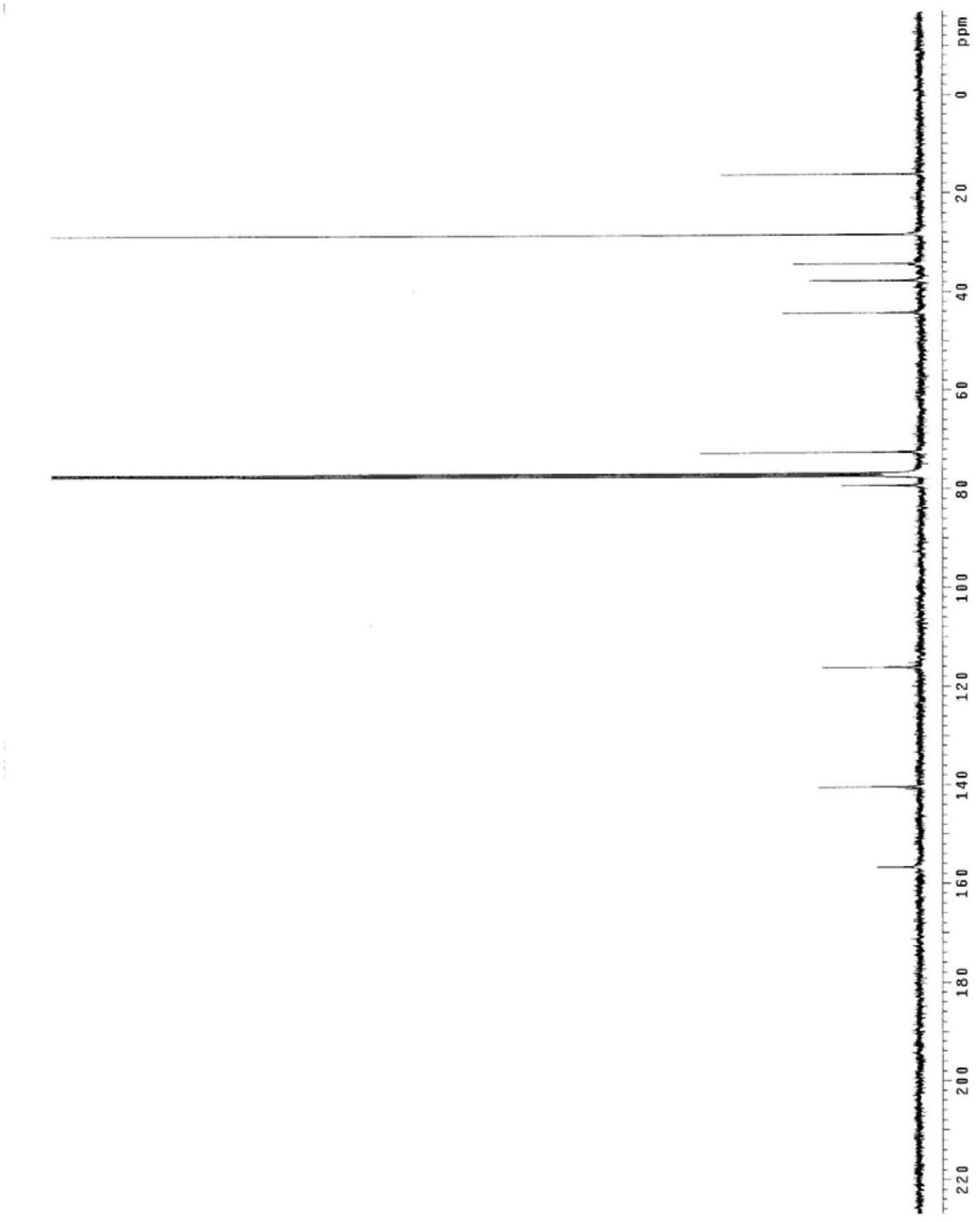
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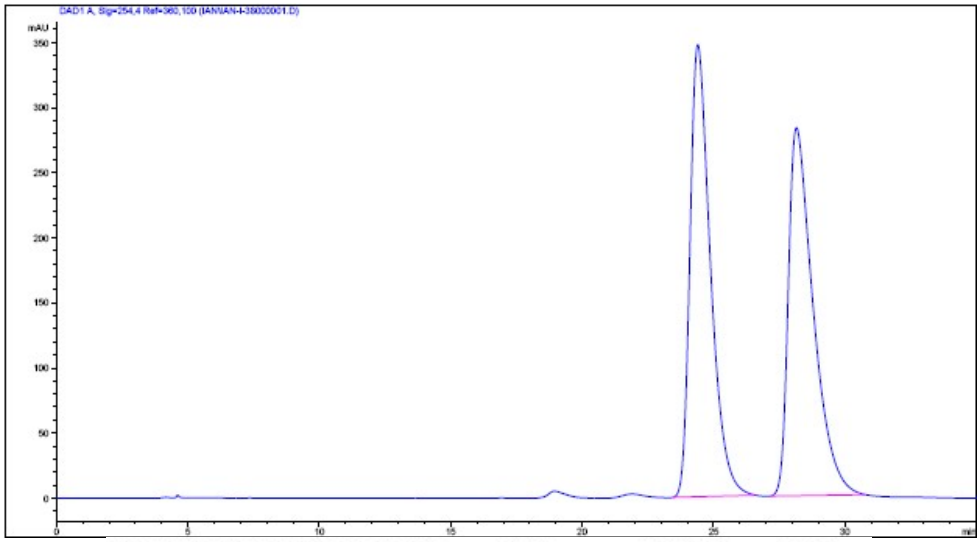
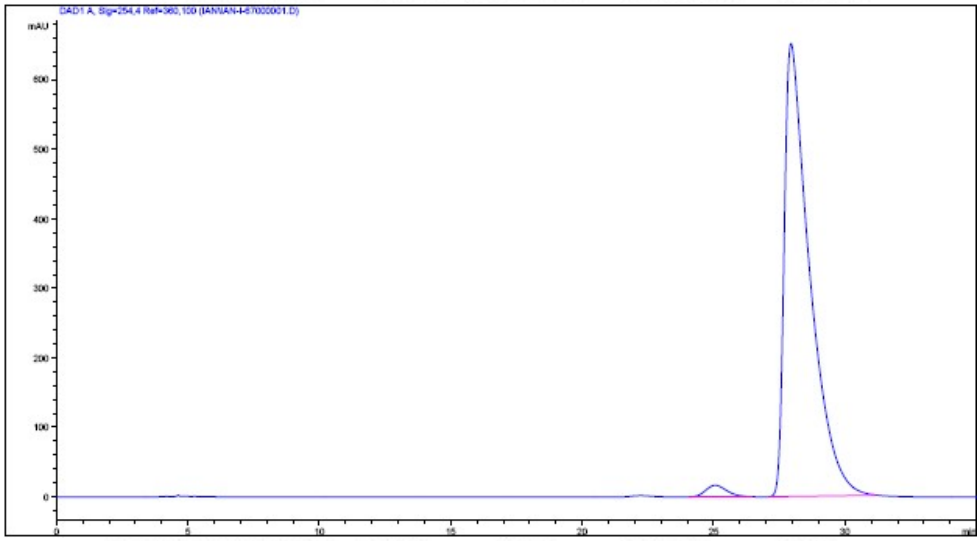
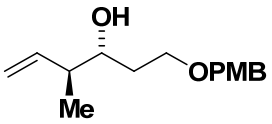


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.394	BB	0.8231	1.88485e4	347.35727	50.3245
2	28.148	BB	0.9777	1.86054e4	282.74048	49.6755



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.055	BB	0.8165	947.26202	16.73059	2.1209
2	27.941	BB	0.9663	4.37170e4	651.95068	97.8791

(*3R*,*4S*)-1-(4-methoxybenzyloxy)-4-methylhex-5-en-3-ol 4.1.4f



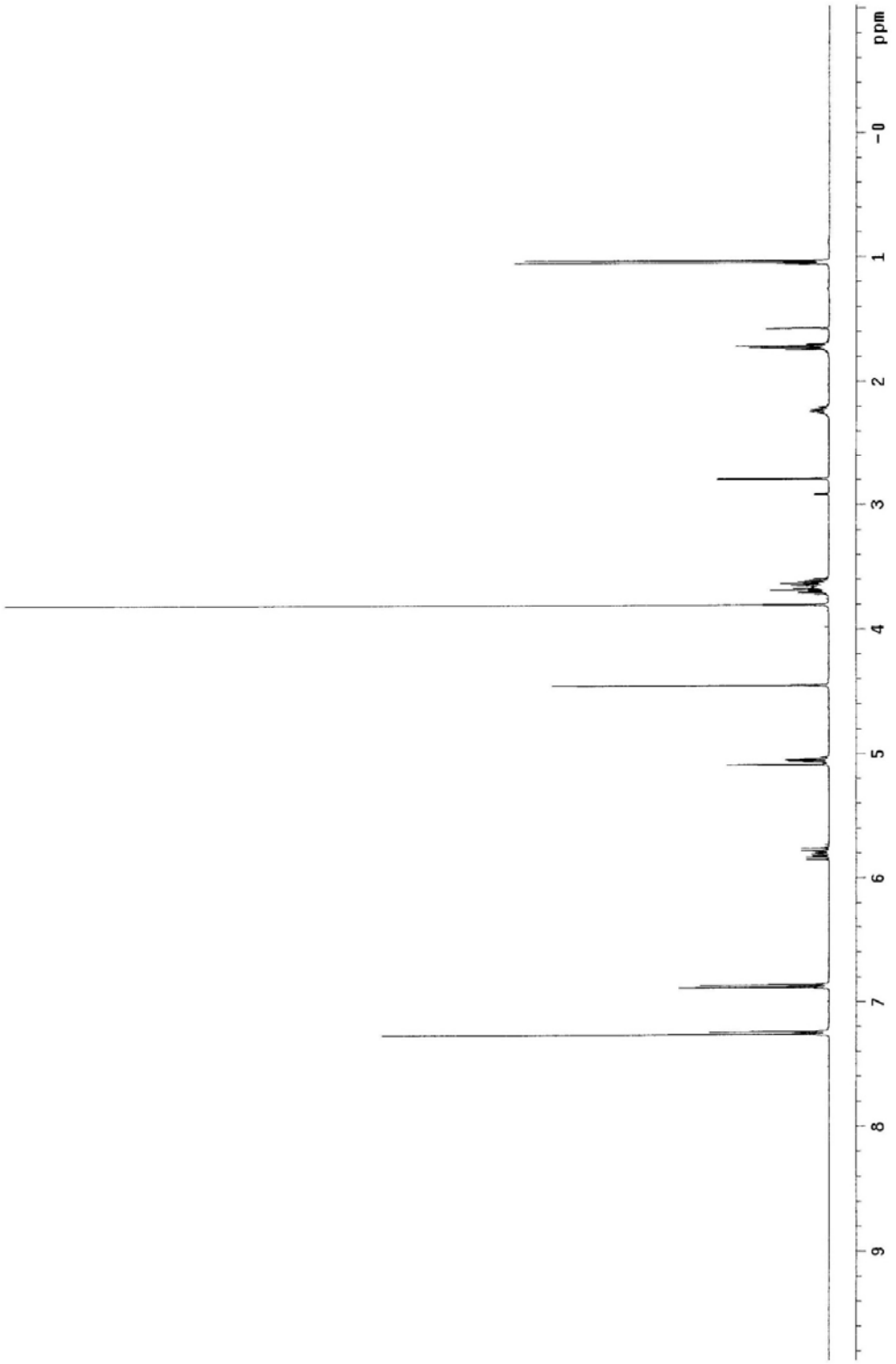
An oven-dried sealed tube under an atmosphere of N_2 was charged with 3-(4-methoxybenzyloxy)propan-1-ol **4.1.2i** (39.2 mg, 0.20 mmol, 100 mol%), (*S*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (21.5 mg, 0.10 mmol, 50 mol%), THF (0.1 mL, 2.0 M), and H_2O (18 μL, 1.0 mmol, 500 mol%). But-3-en-2-yl acetate (45.6 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 60 ^oC and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **4.1.4i** (38.1 mg, 0.152 mmol) as a colorless oil in 76% yield (15:1 dr).

TLC (SiO_2): R_f = 0.5 (ethyl acetate:hexanes, 1:4).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.24 (m, 2H), 6.90-6.86 (m, 2H), 5.80 (dt, *J* = 17.2, 10.0 Hz, 1H), 5.09-5.02 (m, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.71-3.61 (m, 3H), 2.79 (d, *J* = 2.8, 1H), 2.23 (qt, *J* = 6.8, 0.8 Hz, 1H), 1.74-1.70 (m, 2H), 1.03 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 140.5, 130.1, 129.3, 115.4, 113.8, 74.3, 73.0, 68.9, 55.3, 44.0, 33.5, 15.8.

HPLC: Enantiomeric excess was determined by HPLC analysis of the 4-nitrobenzoate derivative of the product (Chiralcel AD-H column, hexanes:*i*-PrOH = 98:2, 1.0 mL/min, 210 nm), t_{minor} = 15.4 min, t_{major} = 17.9 min; ee = 97%.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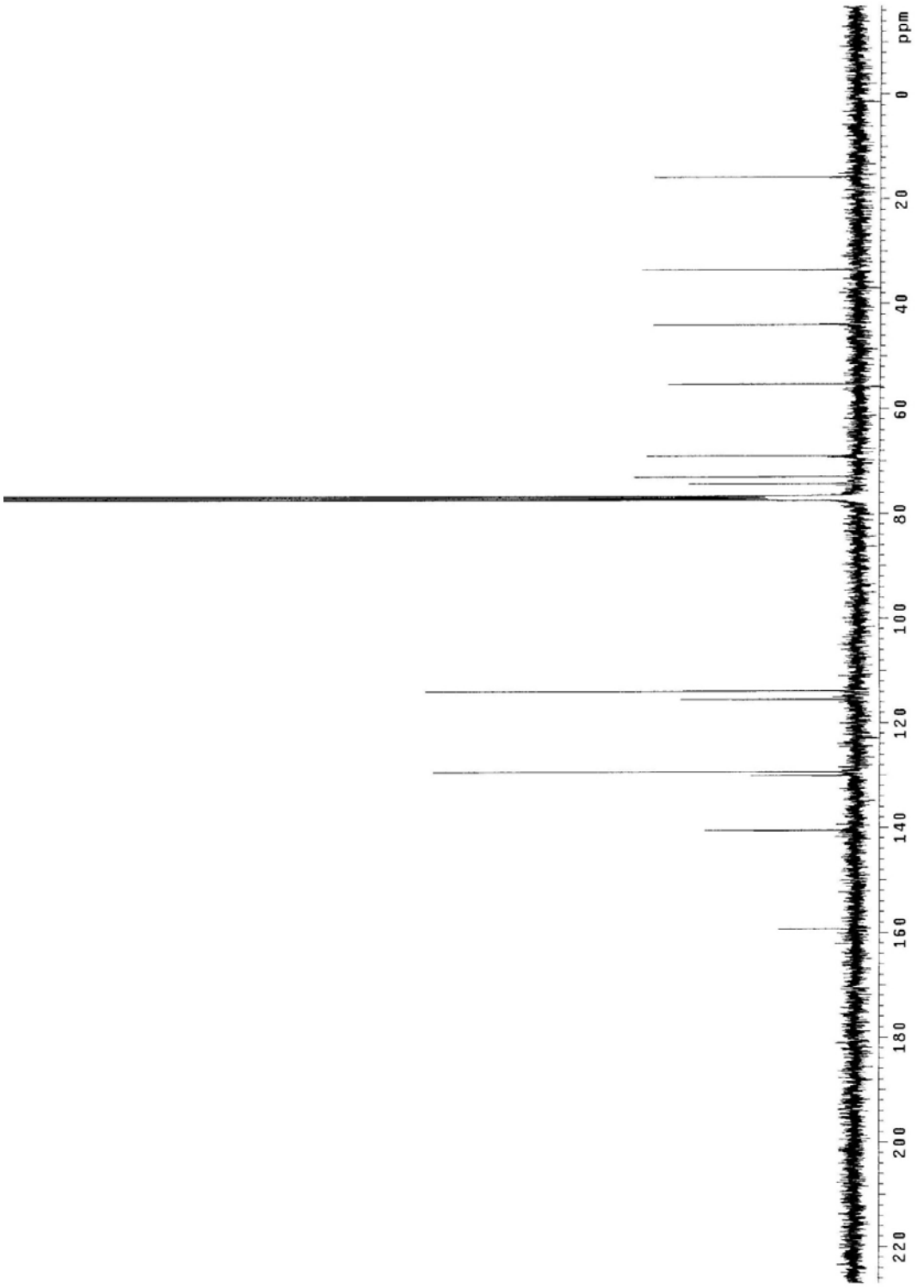
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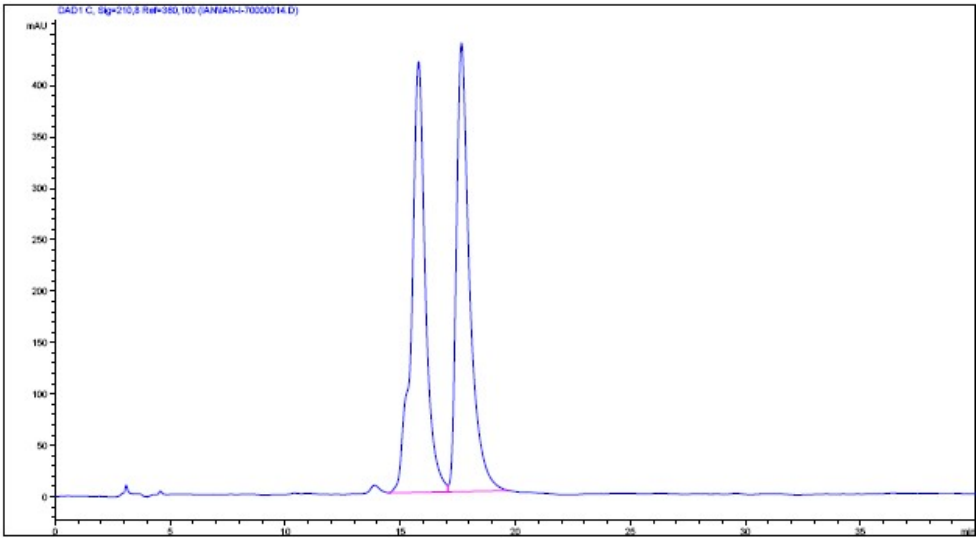

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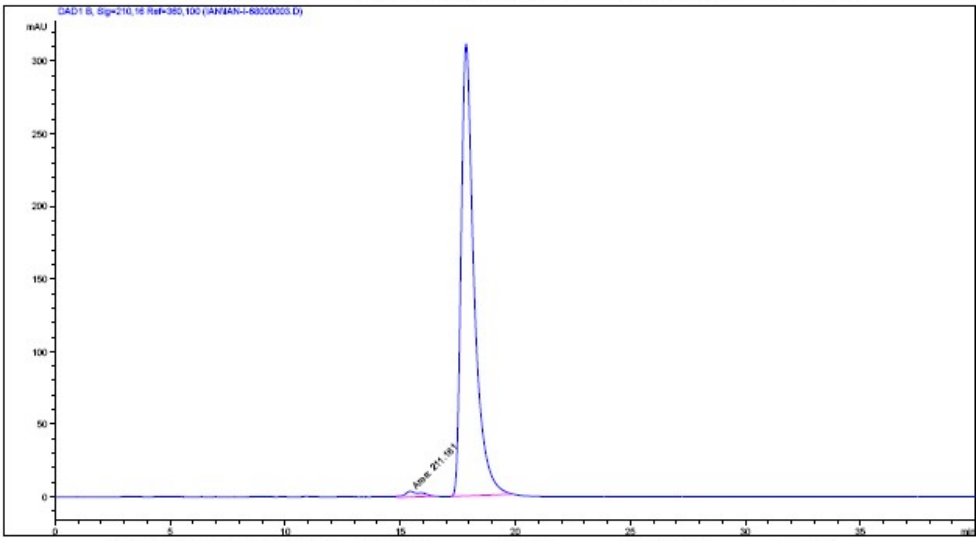
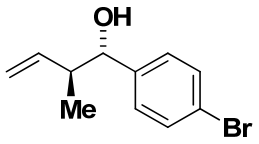
1	15.791	VV	0.6118	1.75273e4	419.21658	50.0536
2	17.658	VB	0.5995	1.74898e4	436.47791	49.9464



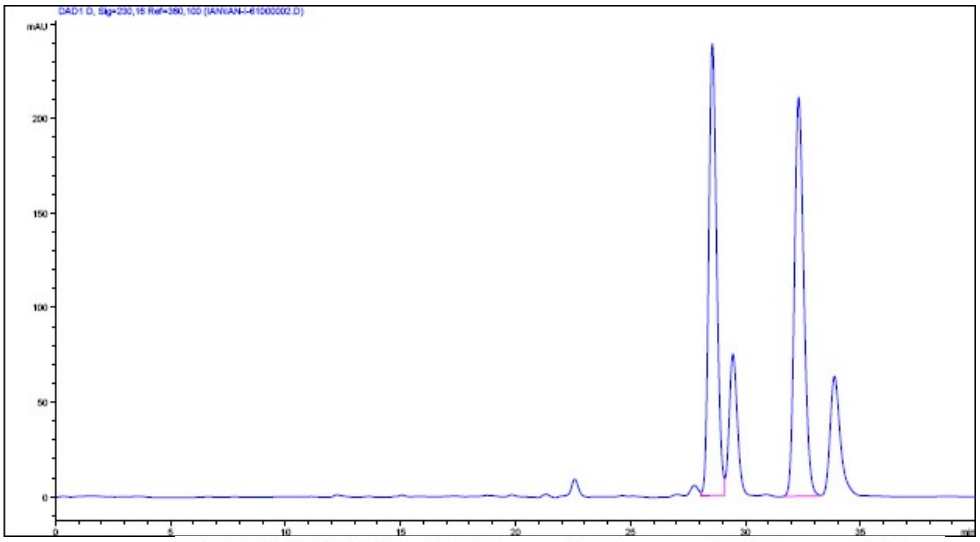
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.432	MM	0.8488	211.18146	4.14648	1.7046
2	17.859	BB	0.5847	1.21779e4	311.11398	98.2954

(*1S*,*2S*)-1-(4-bromophenyl)-2-methylbut-3-en-1-ol 4.1.4a



An oven-dried sealed tube under an atmosphere of N_2 was charged with 4-bromobenzaldehyde **4.1.3a** (37.0 mg, 0.20 mmol, 100 mol%), (*S*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (21.5 mg, 0.10 mmol, 50 mol%), THF (0.1 mL, 2.0 M), isopropanol (31 μL, 0.4 mmol, 200 mol%), and H_2O (18 μL, 1.0 mmol, 500 mol%). But-3-en-2-yl acetate (45.6 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 60 ^oC and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **4.1.4a** (39.5 mg, 0.164 mmol) as a colorless oil in 82% yield (17:1 dr).

HPLC: (Chiralpak AS-H/AS-H column, hexanes:*i*-PrOH = 98:2, 0.5 mL/min, 230 nm), t_{minor} = 27.9 min, t_{major} = 31.8 min; ee = 98%



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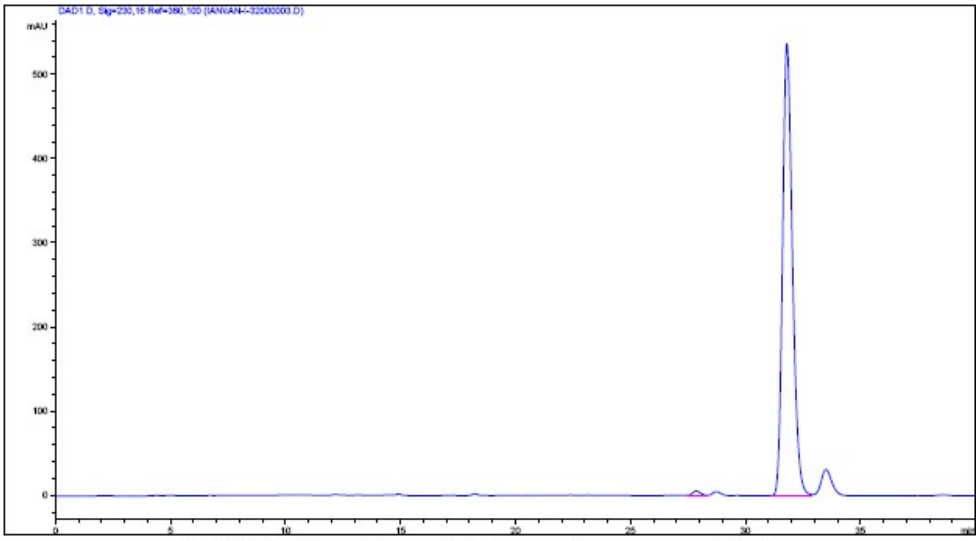
2	32.309	BB	0.4394	5992.81738	210.96976	51.1096



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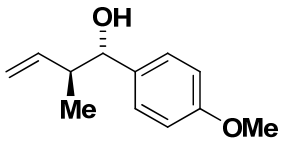
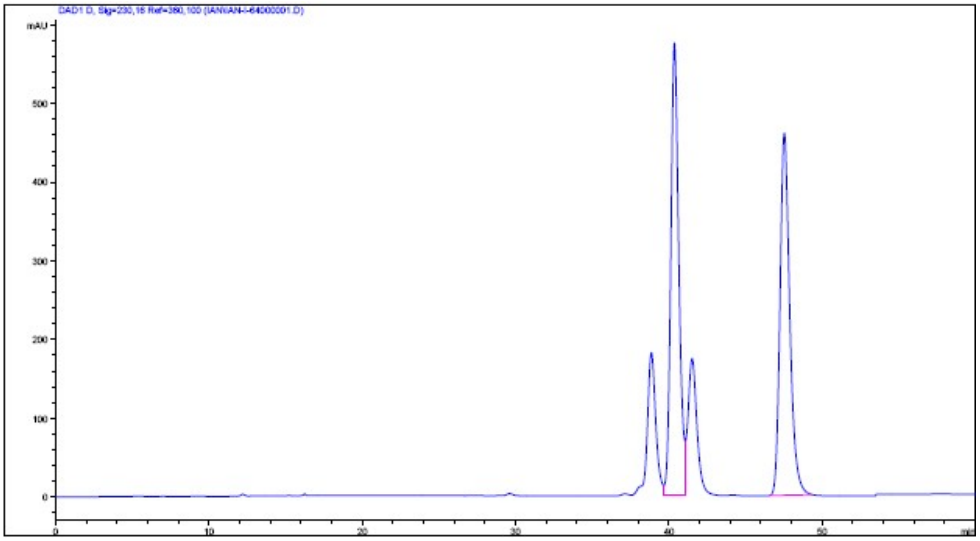
1	27.855	BV	0.3535	122.30916	5.25518	0.7588
2	31.800	BB	0.4577	1.59964e4	536.71680	99.2412

(*1S*,*2S*)-1-(4-methoxyphenyl)-2-methylbut-3-en-1-ol 4.1.4b

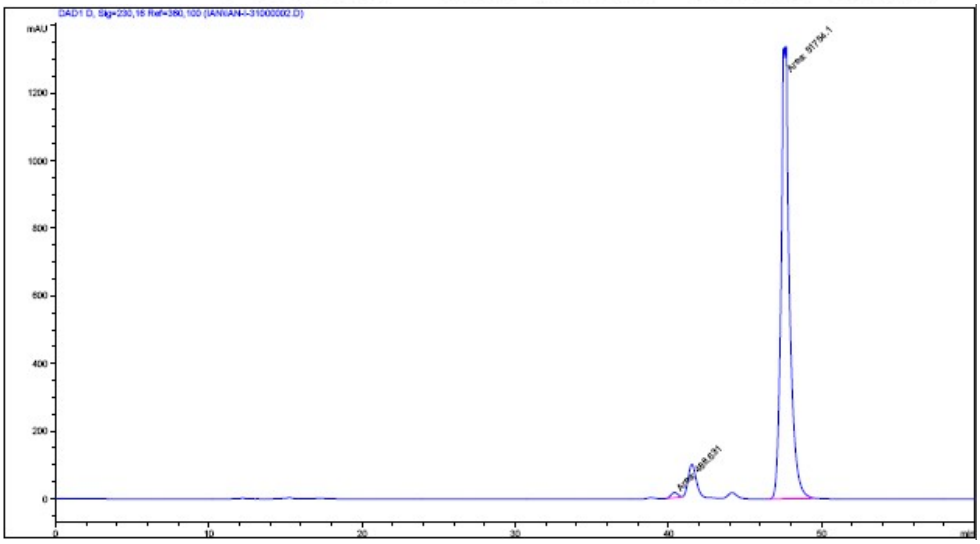


An oven-dried sealed tube under an atmosphere of N_2 was charged with 4-methoxybenzaldehyde **4.1.3b** (27.2 mg, 0.20 mmol, 100 mol%), (*S*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (21.5 mg, 0.10 mmol, 50 mol%), THF (0.1 mL, 2.0 M), isopropanol (31 μL, 0.4 mmol, 200 mol%), and H_2O (18 μL, 1.0 mmol, 500 mol%). But-3-en-2-yl acetate 45.6 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 60 ^oC and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **4.1.4b** (34.2 mg, 0.178 mmol) as a colorless oil in 89% yield (12:1 dr).

HPLC: (Chiralpak AD-H/AD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 230 nm), t_{minor} = 40.2 min, t_{major} = 47.6 min; ee = 98%.

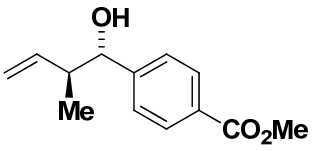


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.362	VV	0.5448	2.08287e4	574.70062	50.6006
2	47.529	BB	0.6652	2.03343e4	460.43875	49.3994



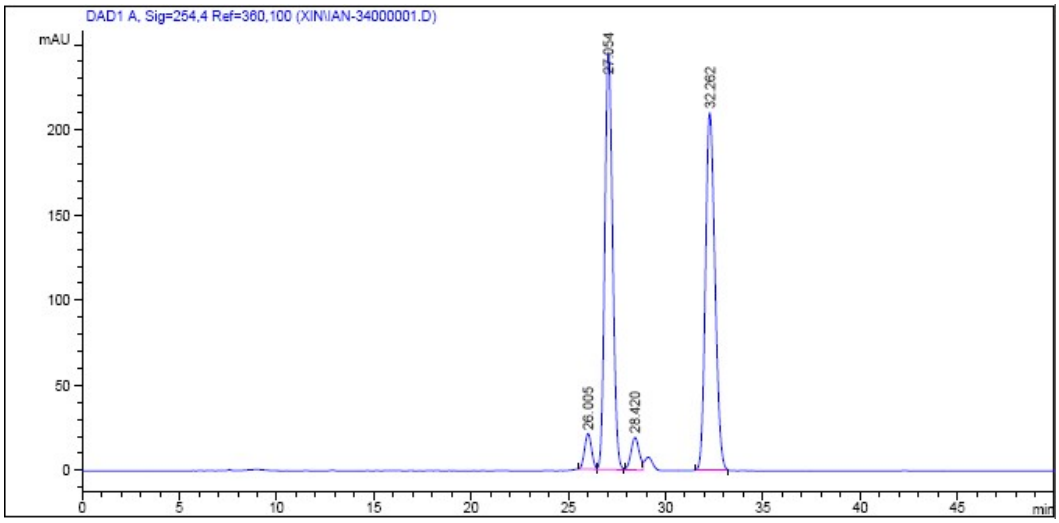
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.395	MM	0.5244	488.63132	15.53036	0.9353
2	47.622	MM	0.6438	5.17541e4	1339.86853	99.0647

Methyl 4-((*1S*,*2S*)-1-hydroxy-2-methylbut-3-enyl)benzoate 4.1.4c

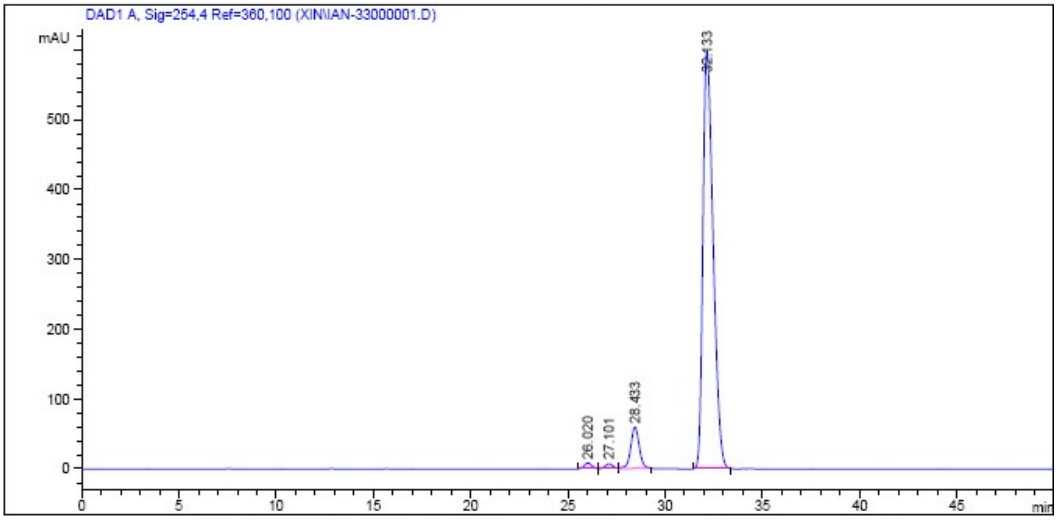


An oven-dried sealed tube under an atmosphere of N_2 was charged with methyl 4-formylbenzoate **4.1.3c** (32.8 mg, 0.20 mmol, 100 mol%), (*S*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (21.5 mg, 0.10 mmol, 50 mol%), THF (0.1 mL, 2.0 M), isopropanol (31 μL, 0.4 mmol, 200 mol%), and H_2O (18 μL, 1.0 mmol, 500 mol%). But-3-en-2-yl acetate (45.6 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 60 ^oC and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **4.1.4c** (35.7 mg, 0.162 mmol) as a colorless oil in 81% yield (11:1 dr).

HPLC: (Chiralpak AD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 254 nm), t_{minor} = 27.1 min, t_{major} = 32.3 min; ee = 98%.

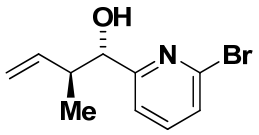


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.005	BV	0.3946	529.10156	20.95080	3.5067
2	27.054	VB	0.4368	6857.31104	244.83498	45.4484
3	28.420	BV	0.4493	565.99902	19.12413	3.7513
4	32.262	BB	0.5267	7135.71631	209.86855	47.2936



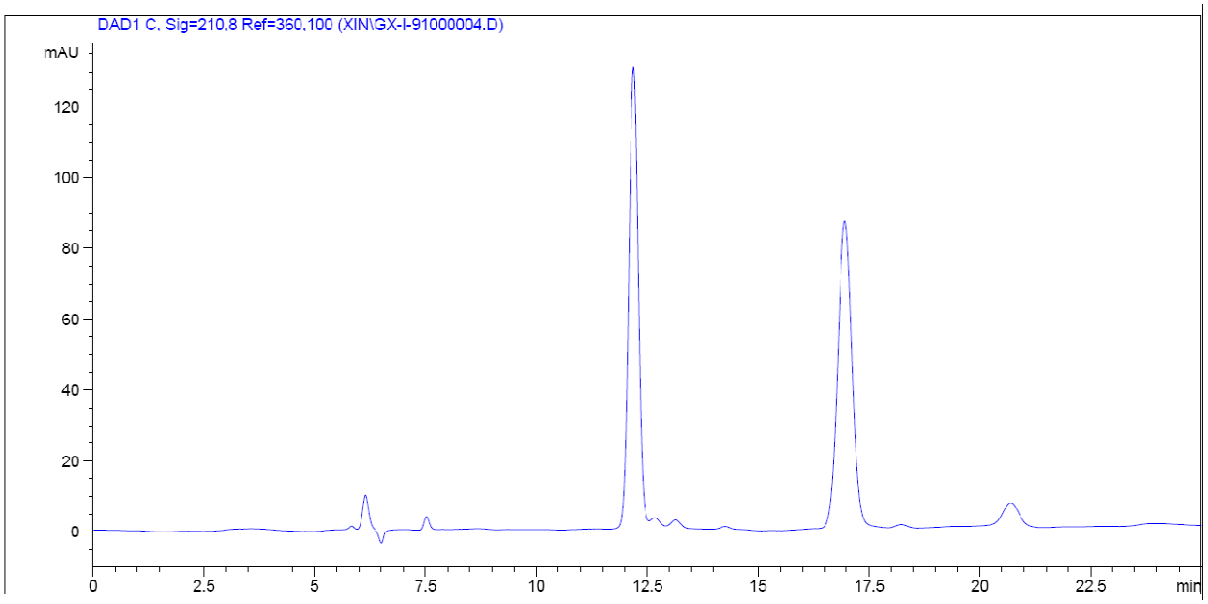
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.020	BV	0.4193	231.31941	8.50547	0.9585
2	27.101	VV	0.4236	193.71434	6.98357	0.8027
3	28.433	VB	0.4696	1836.16467	59.57385	7.6086
4	32.133	BB	0.5662	2.18716e4	598.67102	90.6302

(*1S*,*2S*)-1-(6-bromopyridin-2-yl)-2-methylbut-3-en-1-ol 4.1.4d

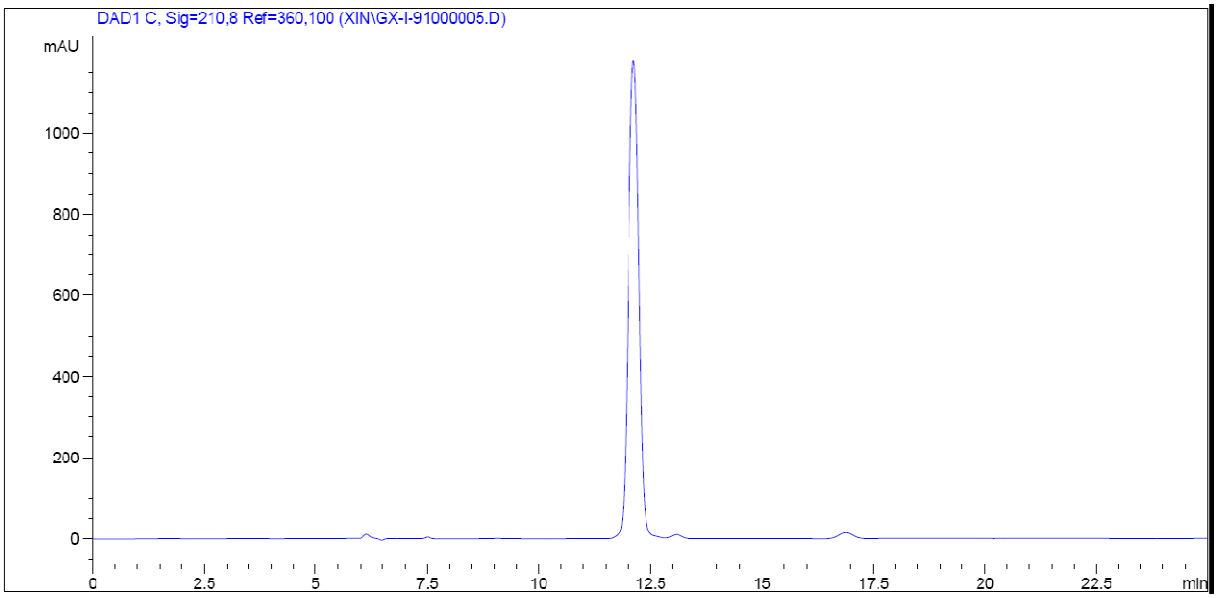


An oven-dried sealed tube under an atmosphere of N_2 was charged with 6-bromopicolinaldehyde **4.1.3d** (37.2 mg, 0.20 mmol, 100 mol%), (*S*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (21.5 mg, 0.10 mmol, 50 mol%), THF (0.1 mL, 2.0 M), isopropanol (31 μL, 0.4 mmol, 200 mol%), and H_2O (18 μL, 1.0 mmol, 500 mol%). But-3-en-2-yl acetate (45.6 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 60 ^oC and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **4.1.4d** (36.3 mg, 0.150 mmol) as a colorless oil in 75% yield (>20:1 dr).

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 210 nm), t_{major} = 12.1 min, t_{minor} = 16.8 min ; ee = 97%.

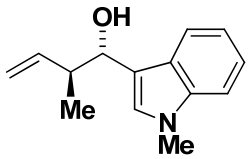


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.186	BV	0.2295	1919.80676	130.59860	49.8528
2	16.951	BB	0.3462	1931.14453	86.57128	50.1472



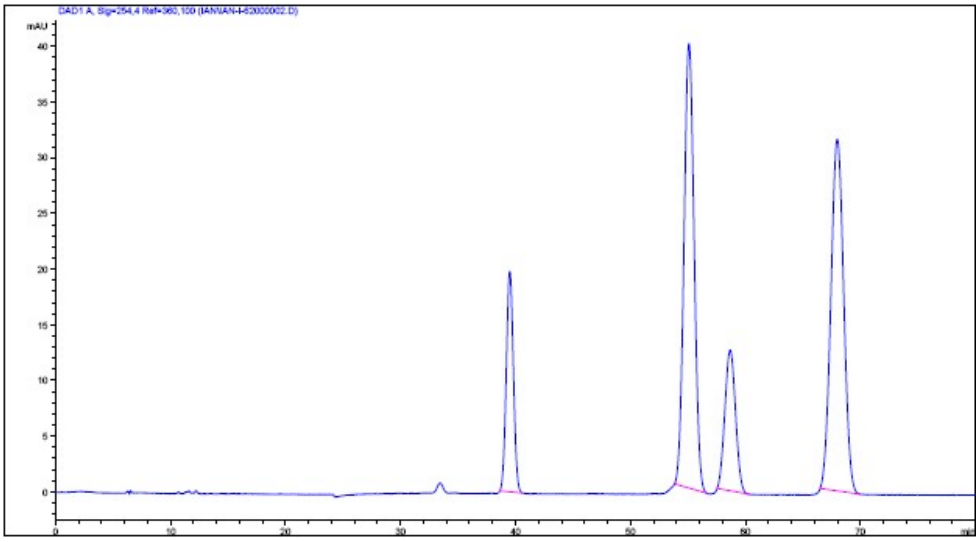
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.118	BB	0.2608	1.92732e4	1178.34497	98.4124
2	16.880	BB	0.3391	310.91425	14.21759	1.5876

(*1S*,*2S*)-2-methyl-1-(1-methyl-1*H*-indol-3-yl)but-3-en-1-ol 4.1.4e

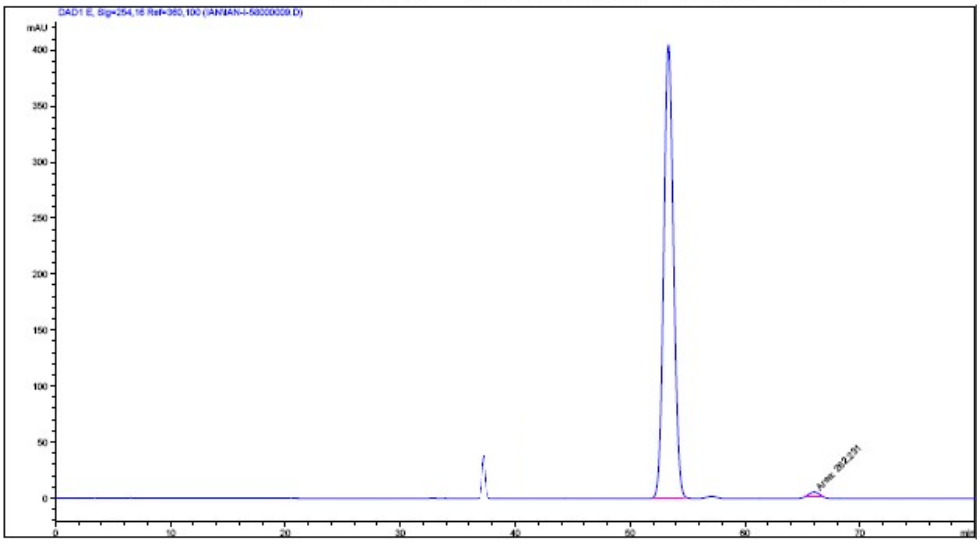


An oven-dried sealed tube under an atmosphere of N_2 was charged with 1-methyl-1*H*-indole-3-carbaldehyde **4.1.3e** (31.8 mg, 0.20 mmol, 100 mol%), (*S*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (21.5 mg, 0.10 mmol, 50 mol%), THF (0.1 mL, 2.0 M), isopropanol (31 μL, 0.4 mmol, 200 mol%), and H_2O (18 μL, 1.0 mmol, 500 mol%). But-3-en-2-yl acetate (45.6 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 60 ^oC and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **4.1.4e** (31.9 mg, 0.148 mmol) as a colorless oil in 75% yield (10:1 dr).

HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 93:7, 0.5 mL/min, 254 nm), t_{major} = 53.3 min, t_{minor} = 66.0 min; ee = 98%.

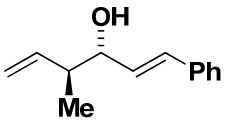


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	39.492	BB	0.6589	850.65906	19.81396	13.0118
2	55.079	BB	0.9157	2436.11816	39.93385	37.2632
3	58.665	BB	0.8004	813.51562	12.64772	12.4437
4	67.979	BB	1.0884	2437.29663	31.58078	37.2813



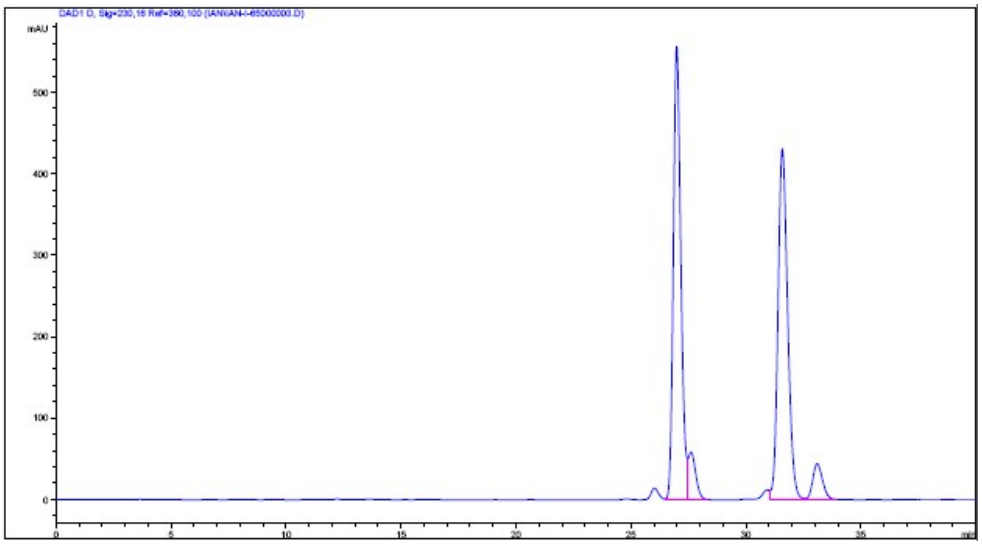
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	53.326	BB	0.9154	2.38488e4	404.75348	98.9124
2	66.016	MM	0.9653	262.23096	4.52740	1.0876

(*3R*,*4S*,*E*)-4-methyl-1-phenylhexa-1,5-dien-3-ol 4.1.4f

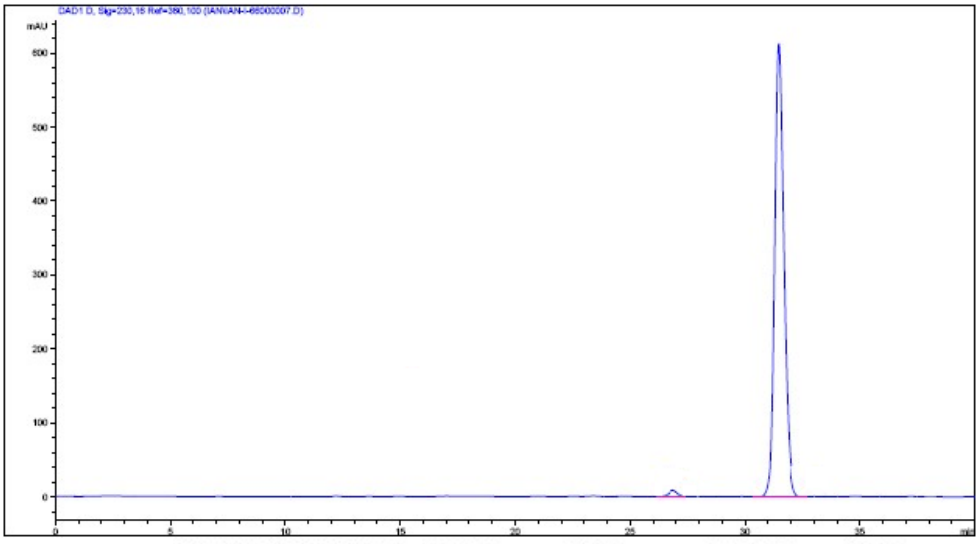


An oven-dried sealed tube under an atmosphere of N_2 was charged with *trans*-cinnamyl aldehyde **4.1.3f** (26.4 mg, 0.20 mmol, 100 mol%), (*S*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (21.5 mg, 0.10 mmol, 50 mol%), THF (0.1 mL, 2.0 M), isopropanol (31 μL, 0.4 mmol, 200 mol%), and H_2O (18 μL, 1.0 mmol, 500 mol%). But-3-en-2-yl acetate (45.6 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **4.1.4f** (29.0 mg, 0.154 mmol) as a colorless oil in 77% yield (10:1 dr).

HPLC: (Chiralpak AS-H/AS-H column, hexanes:*i*-PrOH = 98:2, 0.5 mL/min, 254 nm), t_{minor} = 26.8 min, t_{major} = 31.5 min; ee = 98%.

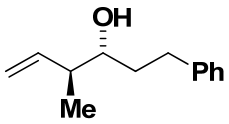


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.987	VV	0.3475	1.26759e4	557.10522	45.5873
2	27.611	VB	0.3413	1330.46252	58.51318	4.7848
3	31.580	VB	0.4475	1.25149e4	430.09030	45.0083
4	33.097	BB	0.4564	1284.49683	43.77251	4.6195



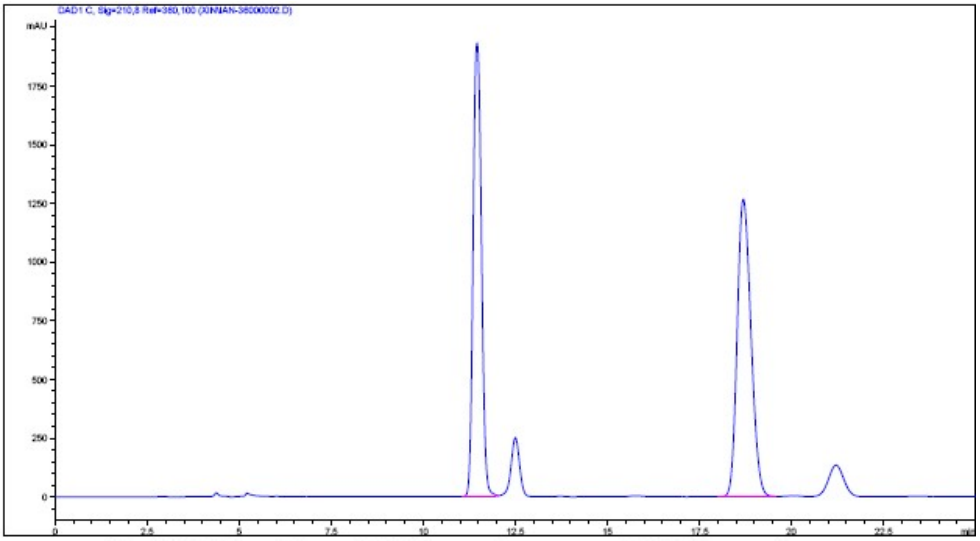
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.800	BV	0.3580	190.00429	10.05732	1.0683
2	31.501	BB	0.4995	1.75957e4	610.08494	98.9317

(*3R*,*4S*)-4-methyl-1-phenylhex-5-en-3-ol 4.1.4g

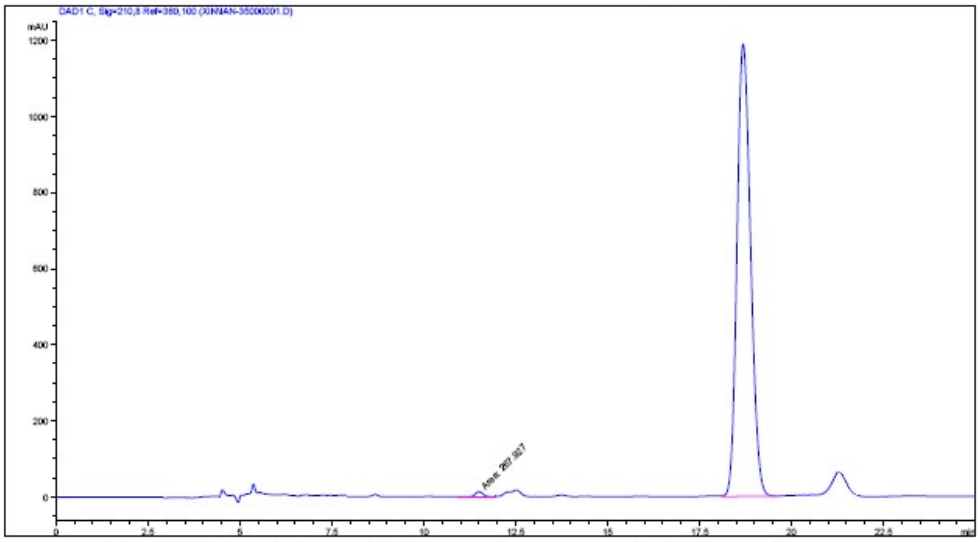


An oven-dried sealed tube under an atmosphere of N_2 was charged with 3-phenylpropanal **4.1.3g** (26.8 mg, 0.20 mmol, 100 mol%), (*S*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (21.5 mg, 0.10 mmol, 50 mol%), THF (0.1 mL, 2.0 M), isopropanol (31 μL, 0.4 mmol, 200 mol%), and H_2O (18 μL, 1.0 mmol, 500 mol%). But-3-en-2-yl acetate (45.6 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 60 ^oC and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **4.1.4g** (27.0 mg, 0.142 mmol) as a colorless oil in 71% yield (>20:1 dr).

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 97:3, 0.7 mL/min, 254 nm), t_{minor} = 11.2 min, t_{major} = 17.4 min; ee = 98%.

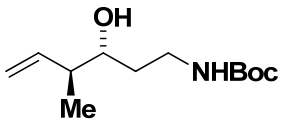


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.459	BV	0.2517	3.04228e4	1932.34814	47.9834
2	18.694	VB	0.4076	3.29800e4	1267.50708	52.0166



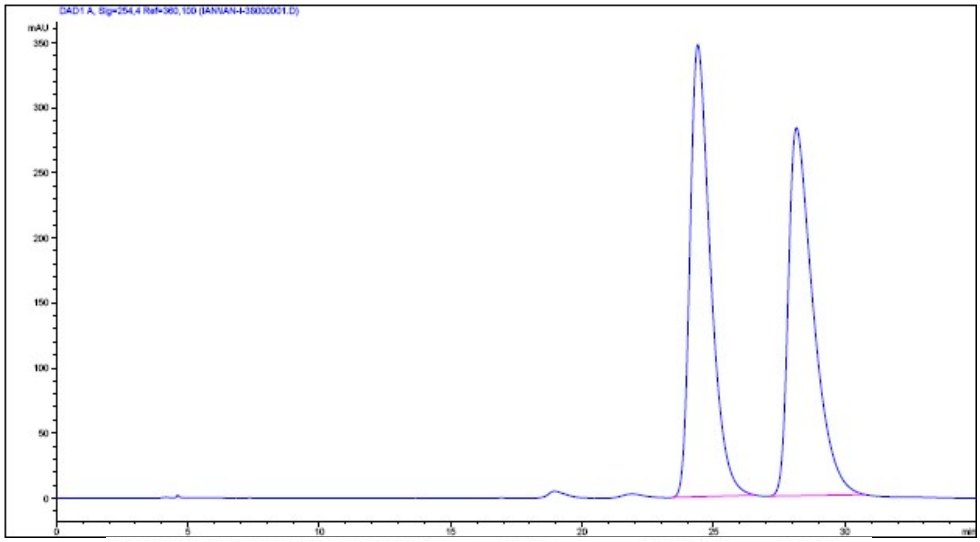
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.503	MM	0.3098	267.92664	14.41337	0.8685
2	18.685	BB	0.4019	3.05811e4	1189.62244	99.1315

***tert*-butyl (*3R,4S*)-3-hydroxy-4-methylhex-5-enylcarbamate 4.1.4h**

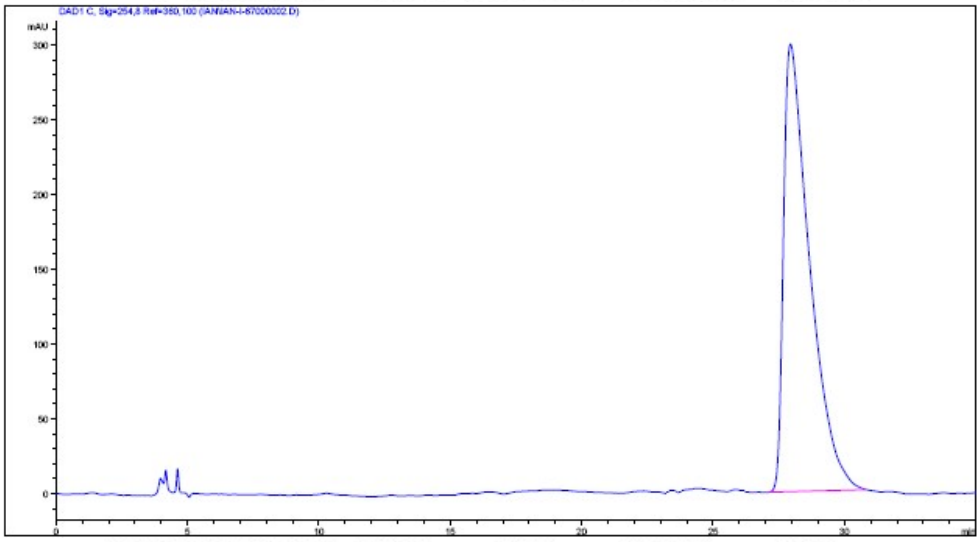


An oven-dried sealed tube under an atmosphere of N_2 was charged with *tert*-butyl 3-oxopropylcarbamate **4.1.3h** (34.6 mg, 0.20 mmol, 100 mol%), (*S*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (21.5 mg, 0.10 mmol, 50 mol%), THF (0.1 mL, 2.0 M), isopropanol (31 μL, 0.4 mmol, 200 mol%), and H_2O (18 μL, 1.0 mmol, 500 mol%). But-3-en-2-yl acetate (45.6 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 70 ^oC and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **4.1.4h** (30.3 mg, 0.142 mmol) as a colorless oil in 66% yield (>20:1 dr).

HPLC: Enantiomeric excess was determined by HPLC analysis of the 4-nitrobenzoate derivative of the product (Chiralcel OJ-H column, hexanes:*i*-PrOH = 98:2, 0.75 mL/min, 254 nm), t_{minor} = 24.4 min, t_{major} = 28.1 min; ee = 99%.

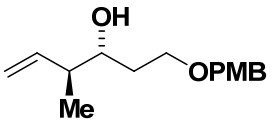


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.394	BB	0.8231	1.88485e4	347.35727	50.3245
2	28.148	BB	0.9777	1.86054e4	282.74048	49.6755



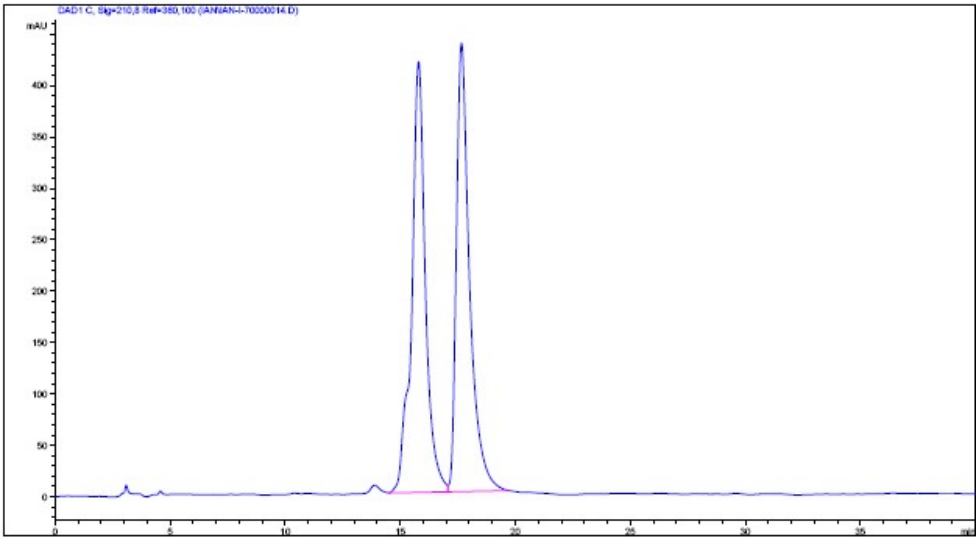
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.941	BB	0.9825	2.07452e4	299.35754	100.0000

(*3R*,*4S*)-1-(4-methoxybenzyloxy)-4-methylhex-5-en-3-ol 4.1.4i

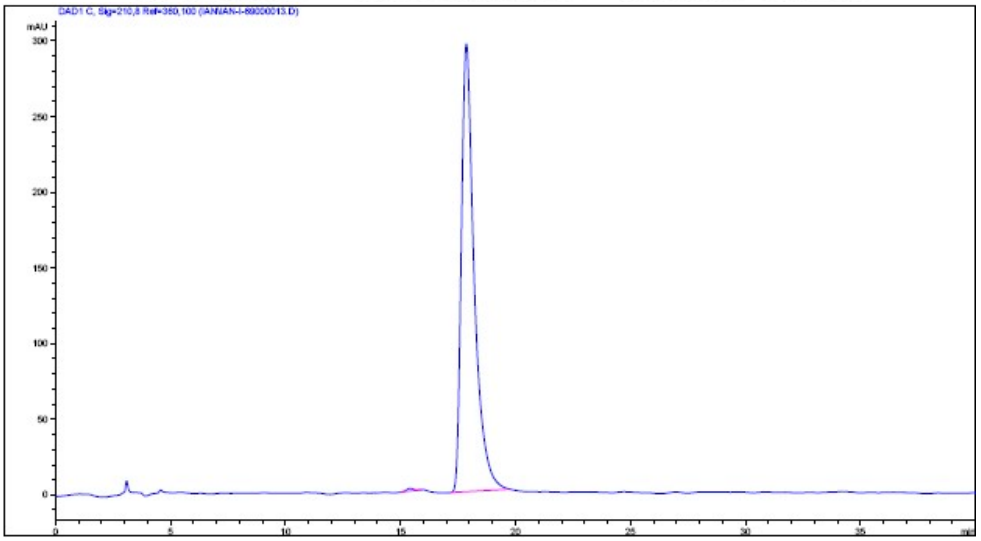


An oven-dried sealed tube under an atmosphere of N_2 was charged with 3-(4-methoxybenzyloxy)propanal **4.1.3i** (38.8 mg, 0.20 mmol, 100 mol%), (*S*)-**I** (10.3 mg, 0.01 mmol, 5 mol%), K_3PO_4 (21.5 mg, 0.10 mmol, 50 mol%), THF (0.1 mL, 2.0 M), isopropanol (31 μL, 0.4 mmol, 200 mol%), and H_2O (18 μL, 1.0 mmol, 500 mol%). But-3-en-2-yl acetate (45.6 mg, 0.40 mmol, 200 mol%) was added and the mixture was allowed to stir at ambient temperature for 0.5 hr, at which point the reaction vessel was placed in an oil bath at 60 ^oC and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 with 0.1% TEA) provided **4.1.4i** (38.1 mg, 0.152 mmol) as a colorless oil in 76% yield (>20:1 dr).

HPLC: Enantiomeric excess was determined by HPLC analysis of the 4-nitrobenzoate derivative of the product (Chiralcel AD-H column, hexanes:*i*-PrOH = 98:2, 1.0 mL/min, 210 nm), t_{minor} = 15.4 min, t_{major} = 17.9 min; ee = 99%.



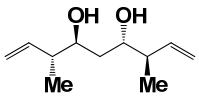
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.791	VV	0.6118	1.75273e4	419.21658	50.0536
2	17.658	VB	0.5995	1.74898e4	436.47791	49.9464



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.420	BB	0.3205	42.41079	1.85682	0.3663
2	17.859	BB	0.5810	1.15342e4	295.77335	99.6337

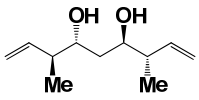
Calculation of Diastereomer Distribution

If mono crotylation : dr = 15:1 er = 99:1 / Syn crotylation : er = 99:1



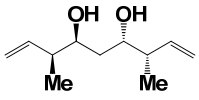
86.14160 %

(15/16)X(99/100)X(15/16)X(99/100)X100
2a



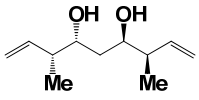
0.00879 %

(15/16)X(1/100)X(15/16)X(1/100)X100
ent-**2a**



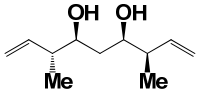
0.38285 %

(1/16)X(99/100)X(1/16)X(99/100)X100
syn,syn-**2b**



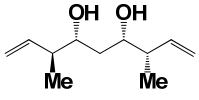
0.00004 %

(1/16)X(1/100)X(1/16)X(1/100)X100
ent-iso-syn,syn-**2b**



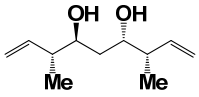
0.11602 %

[(15/16)X(99/100)X(1/16)X(1/100)X100]X2
anti,syn-**2c**



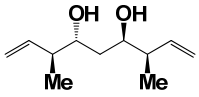
0.11602 %

[(15/16)X(1/100)X(1/16)X(99/100)X100]X2
ent-anti,syn-**2c**



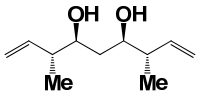
11.48554 %

[(15/16)X(99/100)X(1/16)X(99/100)X100]X2
iso-anti,syn-**2d**



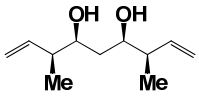
0.00118 %

[(15/16)X(1/100)X(1/16)X(1/100)X100]X2
ent-iso-anti,syn-**2d**



1.74024 %

[(15/16)X(99/100)X(15/16)X(1/100)X100]X2
anti,anti-meso-**2e**

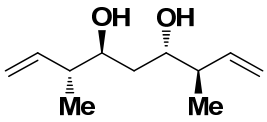


0.00387 %

[(1/16)X(99/100)X(1/16)X(1/100)X100]X2
syn,syn-meso-**2f**

Total % = 99.99615 %

(*3R,4S,6S,7R*)-3,7-Dimethylnona-1,8-diene-4,6-diol 4.2.2a



An oven-dried sealed tube under an atmosphere of N_2 was charged with1,3-propanediol **4.2.1a**(15.2 mg, 0.20 mmol, 100 mol%),(*R*)-**I**(20.7 mg, 0.02 mmol, 10 mol%), Na_2CO_3 (42.4 mg, 0.40 mmol, 200 mol%),and THF (0.2 mL, 1.0 M).Freshly distilled α-methyl allyl acetate (114 mg, 1.00 mmol, 500 mol%) was added and the mixture was allowed to stir at 70^{o}C for 96 hr.The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10) provided **4.2.2a**(28.0 mg, 0.152 mmol) as off-white crystalline solid in 76% yield, ≥ 99% ee, 5:1 dr.

TLC (SiO_2): R_f = 0.3 (ethyl acetate:hexanes, 1:3).

^{1}H NMR(400 MHz, $CDCl_3$): δ 5.79-5.67 (m, 2H), 5.11-5.06 (m, 4H), 3.72-3.65 (m, 2H), 2.61 (br. s, 2H), 2.27-2.18 (m, 2H), 1.57 (dd, *J* = 6.8, 5.2 Hz, 2H), 0.99 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5, 116.1, 71.6, 44.1, 36.6, 16.0.

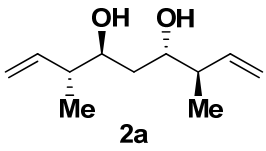
GCCyclosil-B: initial temperature 50 °C (1 min hold); final temperature 200 °C; rate = 5 °C/min; $T_{major\ product}$ = 22.58 min, $T_{minor\ diastereomer}$ = 22.95 min, $T_{minor\ enantiomer}$ = 23.03; ee = 99%, dr = 5:1.

$[\alpha]_D^{27}$ = +56.0 (c = 1.0, CH_2Cl_2).

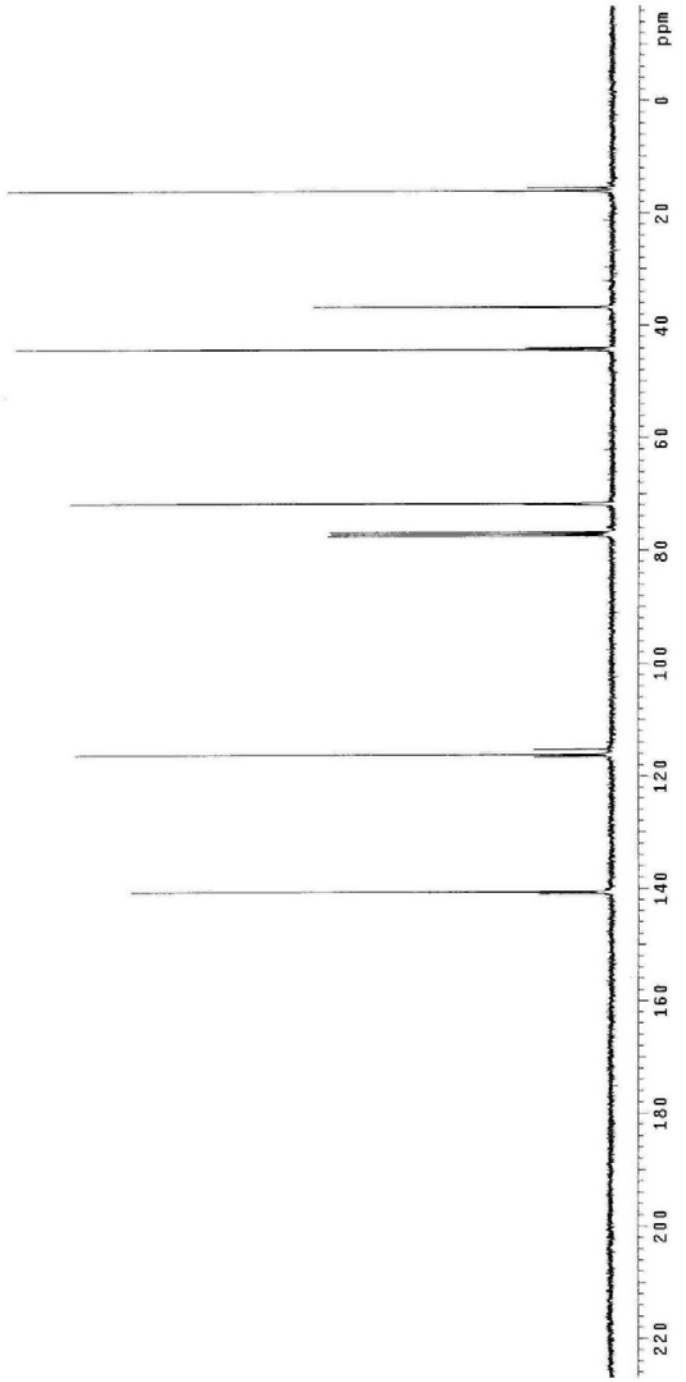
MP = 47–59 ^{o}C

FTIR (neat): υ 3329, 2954, 2916, 1641, 1460, 1404, 1376, 1330, 1290, 1239, 1196, 1173, 1138, 1078, 1032, 1005, 963, 909, 836, 797, 674.

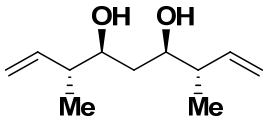
HRMS: (CI) Calcd. for $C_{11}H_{21}O_2$ $[M+H]^+$: 185.1542, Found: 185.1545.



2a


ppm
0
20
40
60
80
100
120
140
160
180
200
220

(*3R,4S,6R,7S*)-3,7-Dimethylnona-1,8-diene-4,6-diol



anti,anti-meso-**2e**

To a solution of (*3S,4R,6S,7R*)-6-(*tert*-butyldimethylsilyloxy)-3,7-dimethylnona-1,8-dien-4-ol (72 mg, 0.24 mmol, 100 mol%) in THF (0.8 mL, 0.25 M) was added TBAF (0.29 mL,1M in THF, 0.29 mmol, 120 mol%). The reaction was stirred at ambient temperature for 1 hr, concentrated under reduced pressure and the residue was subject to flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:3) to provide the title compound (25 mg, 0.14 mmol) as a white crystalline solid in 77% yield.

TLC(SiO_2): R_f = 0.3 (ethyl acetate:hexanes, 1:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81-5.72 (m, 2H), 5.11-5.06 (m, 4H), 3.67 (ddd, *J* = 10.4, 5.6, 2.4 Hz, 2H), 3.12 (br. s, 2H), 2.27-2.18 (m, 2H), 1.63 (dt, *J* = 14.0, 2.0 Hz, 1H), 1.45-1.36 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.1, 116.0, 75.8, 44.5, 36.6.

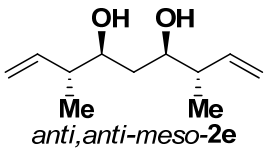
GCCyclosil-B: initial temperature 50 °C (1 min hold); final temperature 200 °C; rate = 5 °C/min; T_{major} = 23.02 min.

MP = 70 - 89°C.

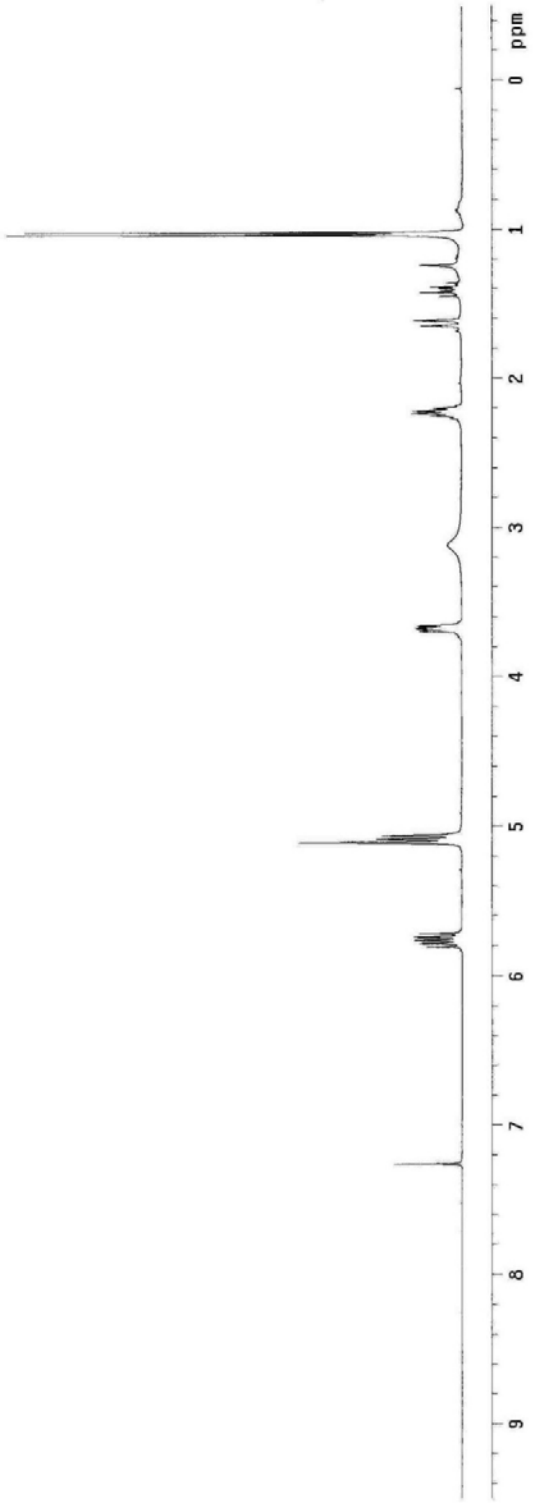
FTIR (neat): υ 3354, 2964, 2928, 2873, 1639, 1458, 1420, 1374, 1324, 1248, 1130, 1047, 1024, 998, 965, 911, 851, 677.

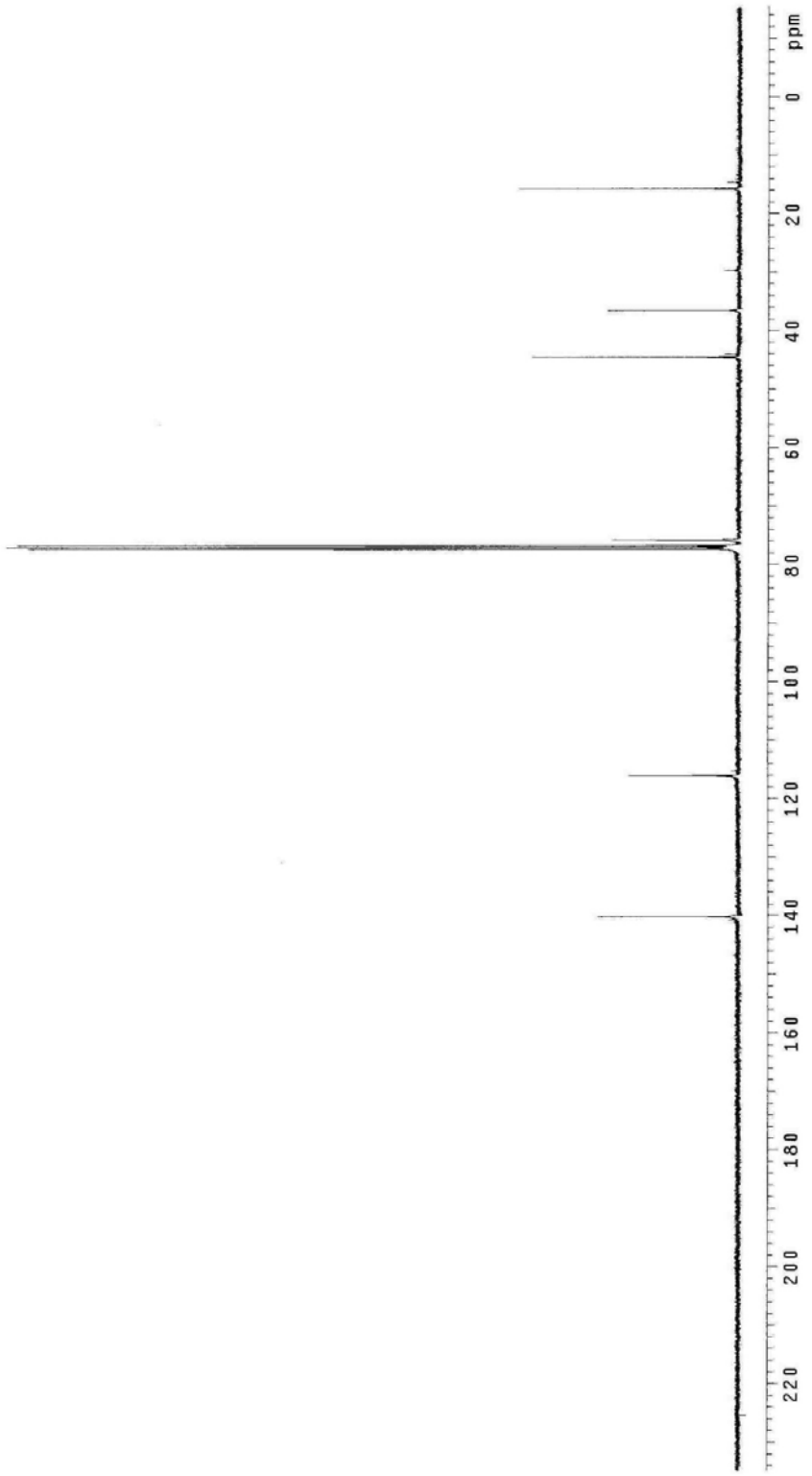
HRMS: (CI) Calcd. for $C_{11}H_{21}O_2$ $[M+H]^+$: 185.1542, Found: 185.1544.

(*Authentic samples 2a & ent-2a were preparedin analogy to the procedure described above.*)



anti,anti-meso-**2e**




ppm
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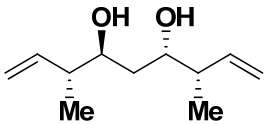
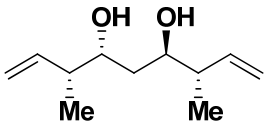
20
40
60
80
100
120
140
160
180
200
220

***rac*-(*3R,4S,6S,7S*)-3,7-Dimethylnona-1,8-diene-4,6-diol**



iso-anti,syn-**2d**



ent-iso-anti,syn-**2d**

A solution of (*3R,4S,6R,7S*)-3,7-dimethylnona-1,8-diene-4,6-diol (30 mg, 0.16 mmol, 100 mol%), PPh_3 (51 mg, 0.20 mmol, 125 mol%) and 4-nitrobenzoic acid (33 mg, 0.20 mmol, 125 mol%) in THF (1.6 mL, 0.1 M) was cooled to 0 °C. Diisopropyl azodicarboxylate (39 μL, 0.20 mmol, 125 mol%) was added to the reaction mixture dropwise. The reaction mixture was stirred at 0 °C for 3 hr, and then allowed to warm to room temperature over 1 hr. The reaction mixture was passed through a short plug of silica gel with the aid of ethyl acetate, and the resulting liquor was concentrated under reduced pressure. The residue was dissolved inmethanol (1.6 mL), K_2CO_3 (28 mg, 0.20 mmol, 125 mol%)was added and the reaction mixture was allowed to stir at ambient temperature for 16 hr. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:5) to provide the racemic title compound (7.0 mg, 0.04 mmol) as an off-white crystalline solid in 23% yield.

TLC(SiO_2): R_f = 0.3 (ethyl acetate:hexanes, 1:3).

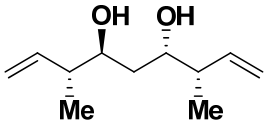
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80-5.68 (m, 2H), 5.16-5.05 (m, 4H), 3.78-3.69 (m, 2H), 2.50 (d, *J* = 4.0 Hz, 1H), 2.33-2.22 (m, 2H), 2.11 (s, 1H), 1.66-1.57 (m, 2H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.8, 140.5, 116.9, 115.3, 72.1, 71.9, 44.5, 43.9, 36.6, 16.2, 15.4.

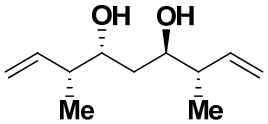
GCCyclosil-B: initial temperature 50 °C (1 min hold); final temperature 200 °C; rate = 5 °C/min; T_1 = 22.91 min, T_2 = 23.28 min.

FTIR (neat): υ 3312, 2979, 2953, 2915, 2866, 1461, 1449, 1405, 1376, 1331, 1097, 1078, 1055, 1032, 1005, 983, 963, 909, 836, 798, 719, 673.

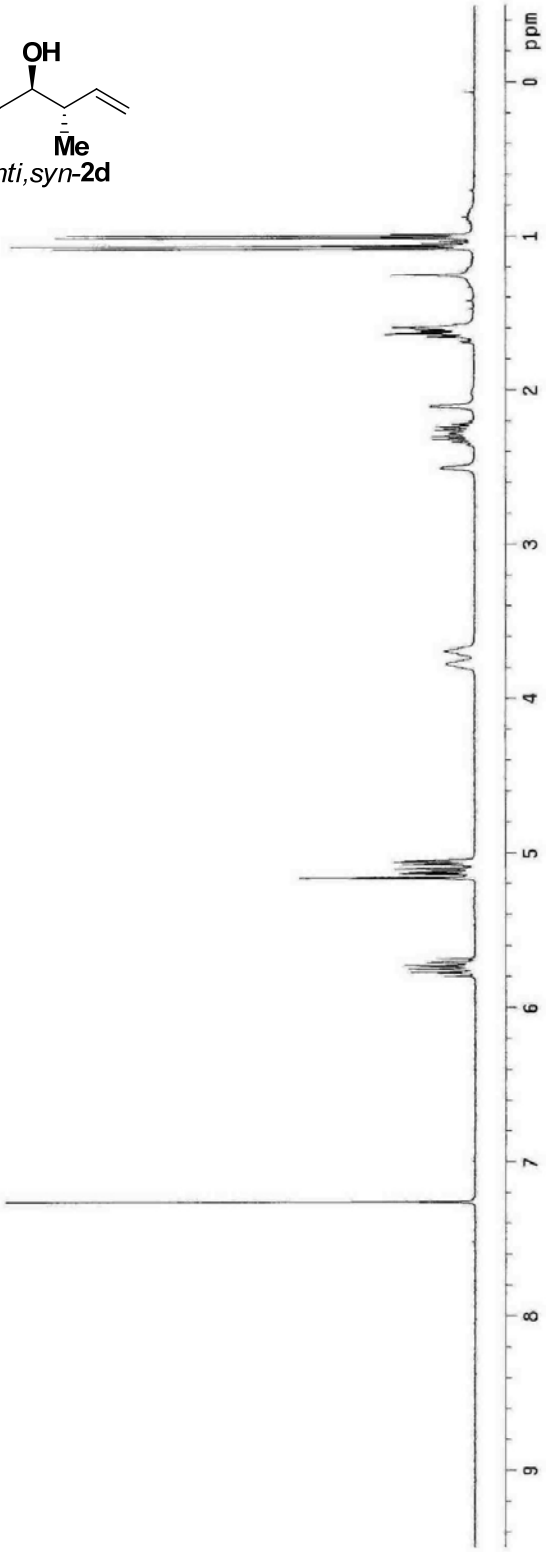
HRMS: (ESI) Calcd. for $C_{11}H_{20}O_2Na$ $[M+Na]^+$: 207.1355, Found: 207.1356.

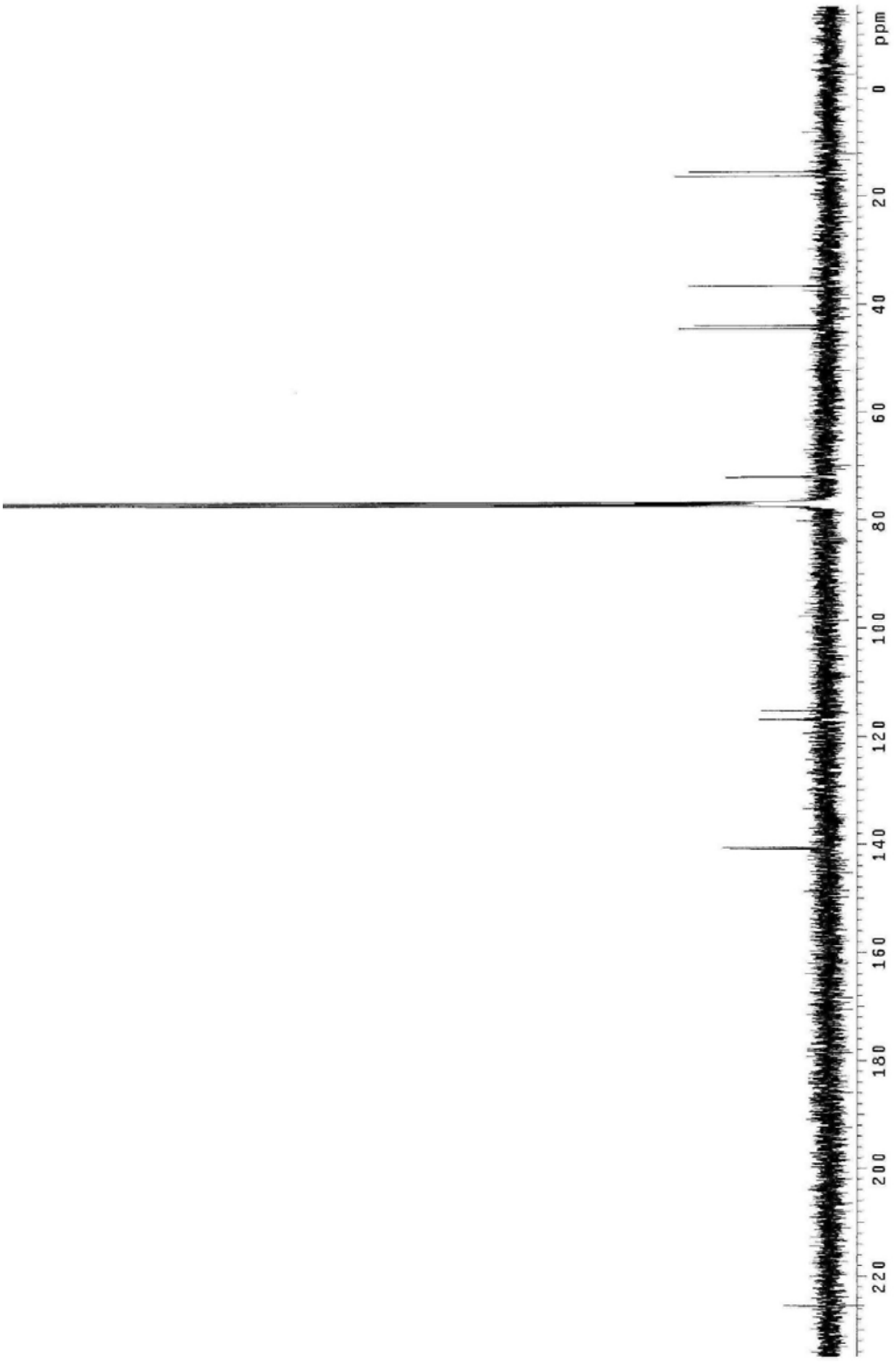


iso-anti,syn-**2d**



ent-iso-anti,syn-**2d**




ppm
0
20
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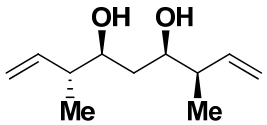
(*3R,4R,6S,7R*)-3,7-Dimethylnona-1,8-diene-4,6-diol



anti,syn-**2c**

A solution of (*3R,4S,6S,7R*)-3,7-dimethylnona-1,8-diene-4,6-diol (40 mg, 0.22 mmol, 100 mol%), PPh_3 (58 mg, 0.22 mmol, 100 mol%) and 4-nitrobenzoic acid (37 mg, 0.22 mmol, 100 mol%) in THF (2.2 mL, 0.1 M) was cooled to 0 °C. Diisopropyl azodicarboxylate (33 μL, 0.22 mmol, 100 mol%) was added to this reaction mixture dropwise. The reaction mixture was stirred at 0 °C for 3 hr, and then allowed to warm to room temperature over 1 hr. The reaction mixture was passed through a short plug of silica gel with the aid of ethyl acetate, and the resulting liquor was concentrated under reduced pressure. The residue was dissolved in methanol (2.2 mL), K_2CO_3 (46 mg, 0.33 mmol, 150 mol%) was added, and the reaction mixture was allowed to stir at ambient temperature for 16 hr. The mixture was then concentrated under reduced pressure, and the residue was subjected to flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:5) to give the title compound (3.0 mg, 0.016 mmol) as an off-white crystalline solid in 7% yield.

TLC(SiO_2): R_f = 0.3 (ethyl acetate:hexanes, 1:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84-5.70 (m, 2H), 5.13-5.05 (m, 4H), 3.75-3.71 (m, 1H), 3.68-3.63 (m, 1H), 3.16-2.89 (br. m, 2H), 2.29-2.19 (m, 2H), 1.67 (dt, *J* = 14.0, 2.4 Hz, 1H), 1.44-1.36 (m, 1H), 1.05-1.02 (m, 6H).

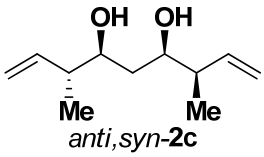
^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7, 140.0, 116.4, 115.4, 76.1, 75.9, 44.7, 44.0, 36.6, 15.8, 14.6.

GCCyclosil-B: initial temperature 50 °C (1 min hold); final temperature 200 °C; rate = 5 °C/min; T_{major} = 23.20 min.

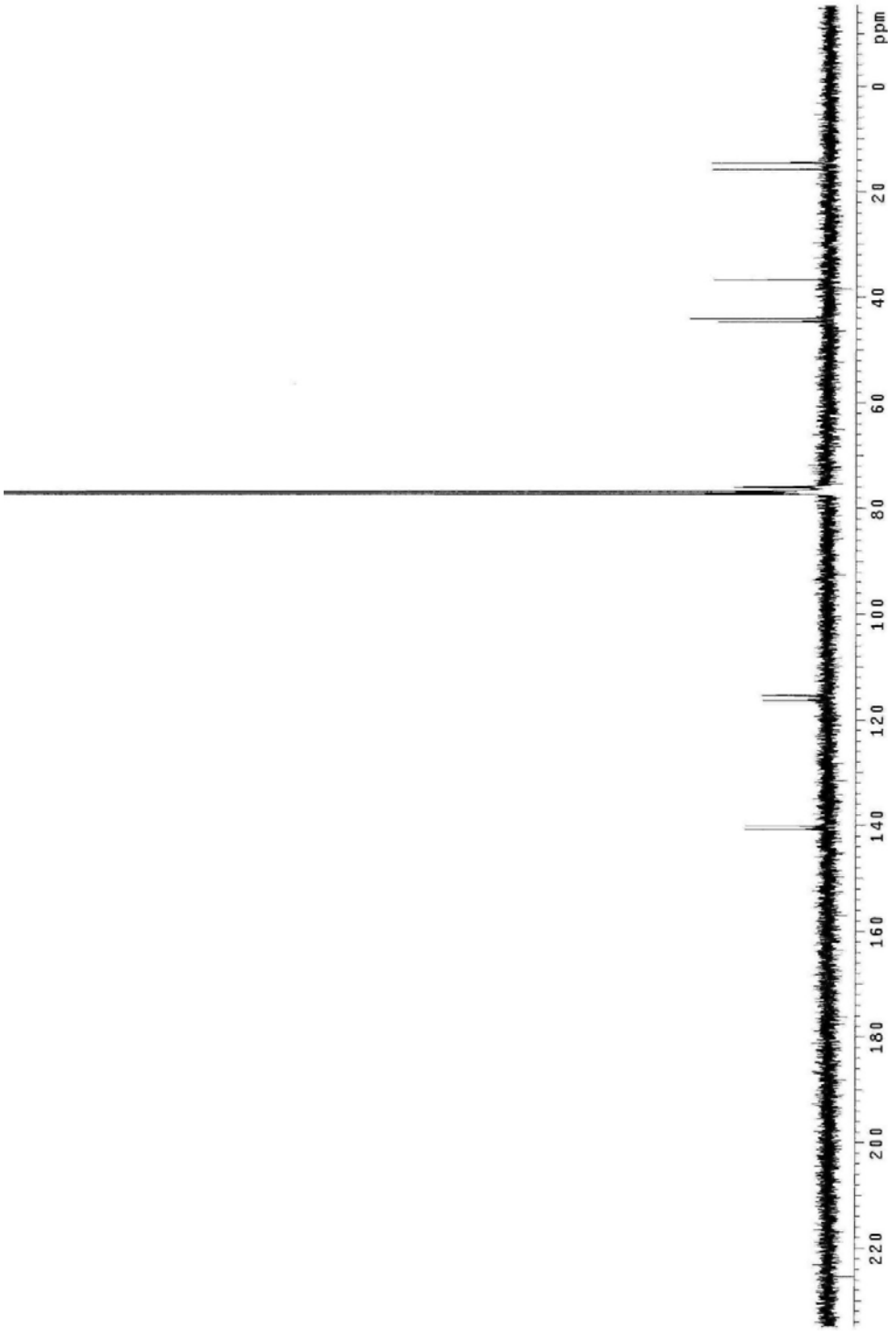
$[\alpha]_D^{27}$ = -25.0 (c = 0.2, CH_2Cl_2).

FTIR (neat): υ 3396, 3369, 2970, 2927, 2877, 2370, 1705, 1653, 1640, 1576, 1460, 1418, 1375, 1108, 1049, 998, 913, 852, 696.

HRMS: (ESI) Calcd. for $C_{11}H_{20}O_2Na$ $[M+Na]^+$: 207.1355, Found: 207.1357.



anti,syn-**2c**


ppm
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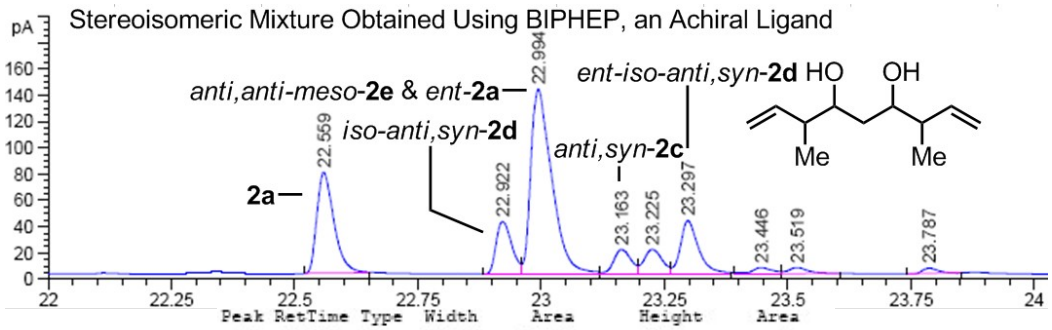
120
140
160
180
200
220

Determination of Diastereomer Ratio and Stereochemistry Confirmation-GC Comparison



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
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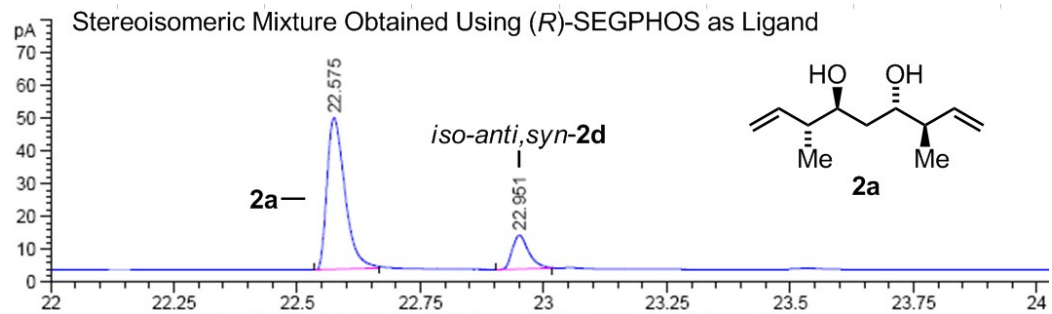
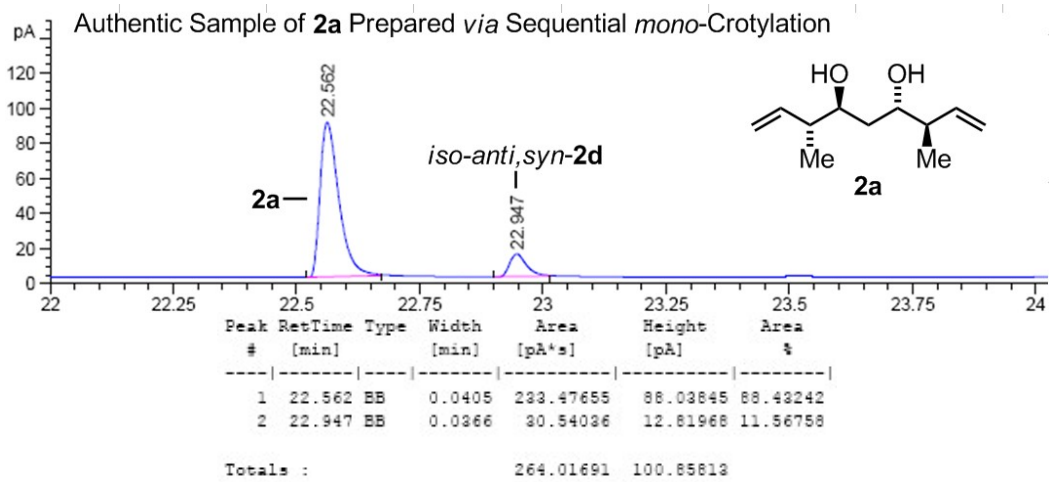
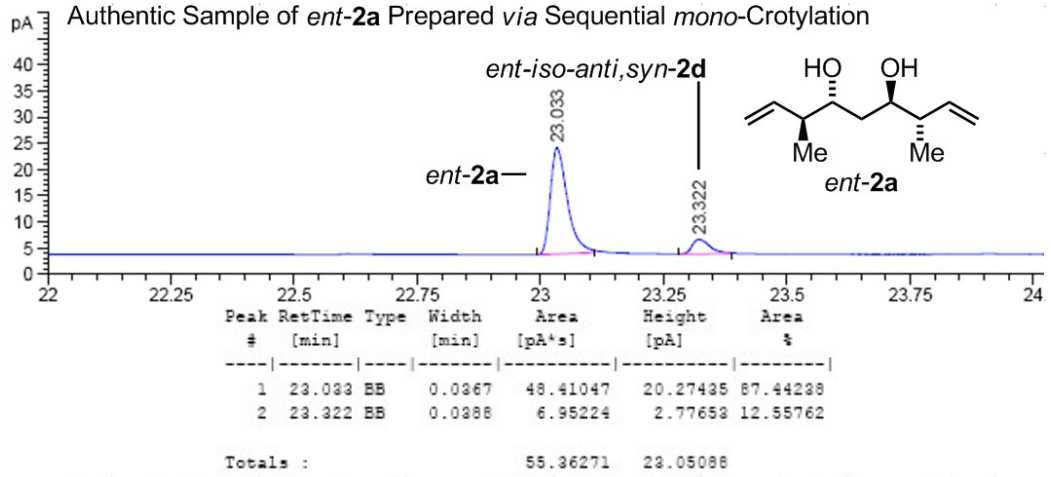
2	22.922	BV	0.0345	87.31375	39.60627	9.49326
3	22.994	VB	0.0435	417.40033	140.47366	45.38220
4	23.163	BV	0.0379	44.66223	18.42192	4.85594
5	23.225	VV	0.0389	47.54790	18.43514	5.16968
6	23.297	VB	0.0377	102.41479	40.28197	11.13513
7	23.446	BV	0.0398	12.84549	4.60050	1.39664
8	23.519	VB	0.0419	12.95843	4.56533	1.40892
9	23.787	BB	0.0356	8.54459	3.83988	0.92902
Totals :				919.74469	347.09404	



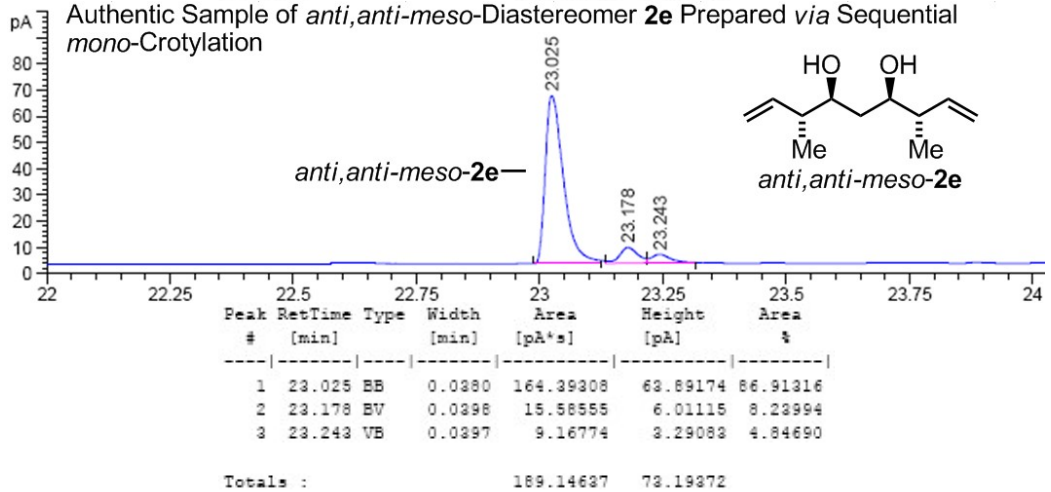
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	22.575	BB	0.0398	116.52431	46.16229	83.07941
2	22.951	BB	0.0357	23.73223	10.28192	16.92059
Totals :				140.25655	56.44421	



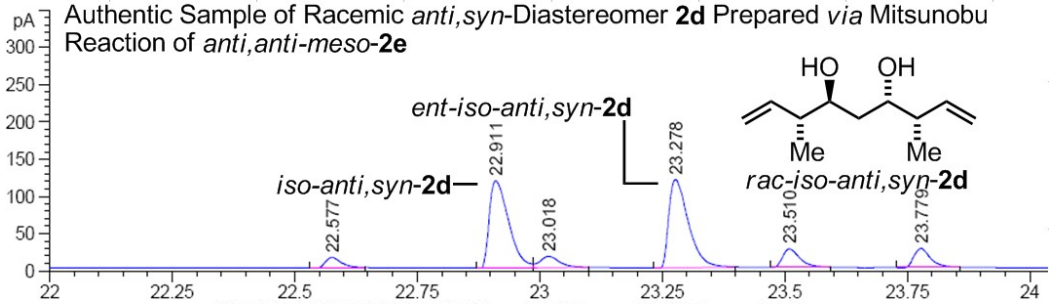
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	22.562	BB	0.0405	233.47655	88.03845	88.43242
2	22.947	BB	0.0366	30.54036	12.81968	11.56758
Totals :				264.01691	100.85813	



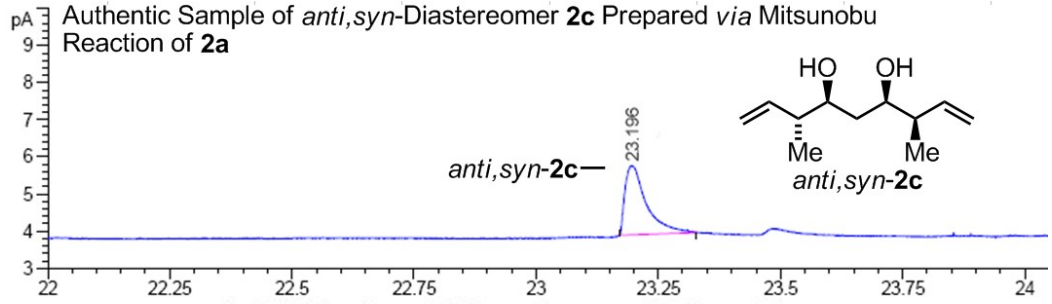
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	23.033	BB	0.0367	48.41047	20.27435	87.44238
2	23.322	BB	0.0388	6.95224	2.77653	12.55762
Totals :				55.36271	23.05088	



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	23.025	BB	0.0380	164.39308	63.89174	86.91316
2	23.178	BV	0.0398	15.58555	6.01115	8.23994
3	23.243	VB	0.0397	9.16774	3.29083	4.84690
Totals :				189.14637	73.19372	



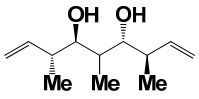
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	22.577	BB	0.0353	31.52443	13.89740	3.75652
2	22.911	BV	0.0406	318.10651	116.75005	37.90630
3	23.018	VB	0.0415	42.78696	15.26539	5.09859
4	23.278	BB	0.0427	326.67844	117.92314	38.92775
5	23.510	BB	0.0374	60.72888	24.77248	7.23659
6	23.779	BB	0.0367	59.36637	25.52904	7.07423
Totals :				839.19159	314.13749	



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	23.196	MM	0.0509	5.68556	1.86075	1.000e2
Totals :				5.68556	1.86075	

Caculation of Diastereomer Distribution

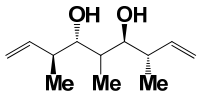
If mono crotylation : dr = 15:1 er = 99:1 / Syn crotylation : er = 99:1



86.14160 %

(15/16)X(99/100)X(15/16)X(99/100)X100

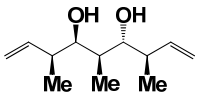
3a



0.00879 %

(15/16)X(1/100)X(15/16)X(1/100)X100

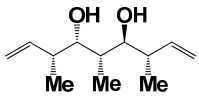
ent-2a



5.74277 %

(15/16)X(1/100)X(1/16)X(99/100)X100

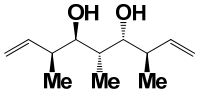
s,s,a,a-3b



0.00059 %

(15/16)X(1/100)X(1/16)X(99/100)X100

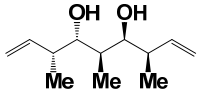
ent-s,s,a,a-3b



5.74277 %

(15/16)X(1/100)X(1/16)X(99/100)X100

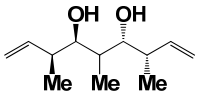
s,a,s,a-3c



0.00059 %

(15/16)X(1/100)X(1/16)X(99/100)X100

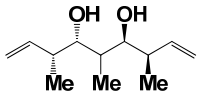
ent-s,a,s,a-3c



0.38285 %

(1/16)X(99/100)X(1/16)X(99/100)X100

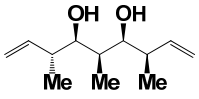
s,s-3d



0.00004 %

(1/16)X(1/100)X(1/16)X(1/100)X100

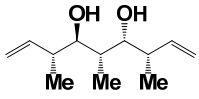
ent-s,s-3d



0.05742 %

(15/16)X(99/100)X(1/16)X(99/100)X100

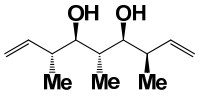
a,s,s,s-3e



0.05742 %

(15/16)X(99/100)X(1/16)X(99/100)X100

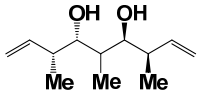
ent-a,s,s,s-3e



0.05742 %

(15/16)X(99/100)X(1/16)X(99/100)X100

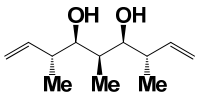
a,a,a,s-3f



0.05742 %

(15/16)X(99/100)X(1/16)X(99/100)X10

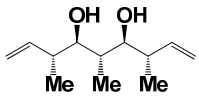
ent-a,a,a,s-3f



0.87011 %

(15/16)X(99/100)X(15/16)X(1/100)X100

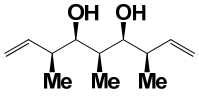
meso-a,s,s,a-3g



0.87011 %

(15/16)X(99/100)X(15/16)X(1/100)X100

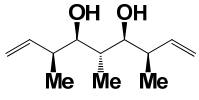
meso-a,a,a,a-3g



0.00387 %

(1/16)X(99/100)X(1/16)X(1/100)X100

meso-s,s,s,s-3g



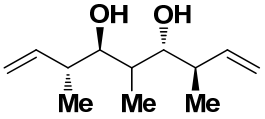
0.00387 %

(1/16)X(99/100)X(1/16)X(1/100)X100

meso-s,a,a,s-3g

Total % = 100.00002 %

(*3R,4S,6S,7R*)-3,7-Dimethylnona-1,8-diene-4,6-diol 4.2.3a



An oven-dried sealed tube under an atmosphere of N_2 was charged with1,3-propanediol **4.2.1b**(18.0 mg, 0.20 mmol, 100 mol%), (*R*)-**I**(20.7 mg, 0.02 mmol, 10 mol%), K_3PO_4 (42.4 mg, 0.20 mmol, 100 mol%),and THF:H_2O (4:1, 0.125 mL, 1.6 M).Freshly distilled crotyl acetate (114 mg, 1.00 mmol, 500 mol%) was added and the mixture was allowed to stir at 70^{o}C for 96 hr.The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10) provides **4.2.3a**(24.6 mg, 0.124 mmol) as off-white crystalline solid in62% yield, ≥ 99% ee, 5:1 dr.

TLC (SiO_2): R_f = 0.3 (ethyl acetate:hexanes, 1:3).

^{1}H NMR(400 MHz, $CDCl_3$): δ5.85-5.73 (m, 2H), 5.15-5.09 (m, 4H), 3.65 (d, *J* = 9.6 Hz, 1H), 3.39-3.37 (m, 1H), 2.80 (s, 1H), 2.54 (d, J = 4.0 Hz, 1H), 2.46-2.40 (m, 1H), 2.31-2.25 (m, 1H), 1.89-1.86 (m, 1H), 1.03 (d, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 1H), 0.94 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ142.2, 141.0, 116.5, 116.0, 79.3, 73.9, 42.3, 42.0, 34.8, 17.2, 16.5, 10.7.

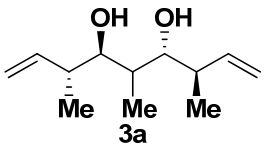
GCCyclosil-B: initial temperature 90 °C (1 min hold); final temperature 140 °C; rate = 1 °C/min; T_{major} = 43.99 min, $T_{minor\ diastereomer\text{-}1}$ = 42.92 min, $T_{minordiastereomer\text{-}2}$ = 46.16 min, $T_{minorenantiomer}$ = 43.99 min; ee = 99%, dr = 6:1.

$[\alpha]_D^{27}$ = +18.9 (c = 0.37, CH_2Cl_2).

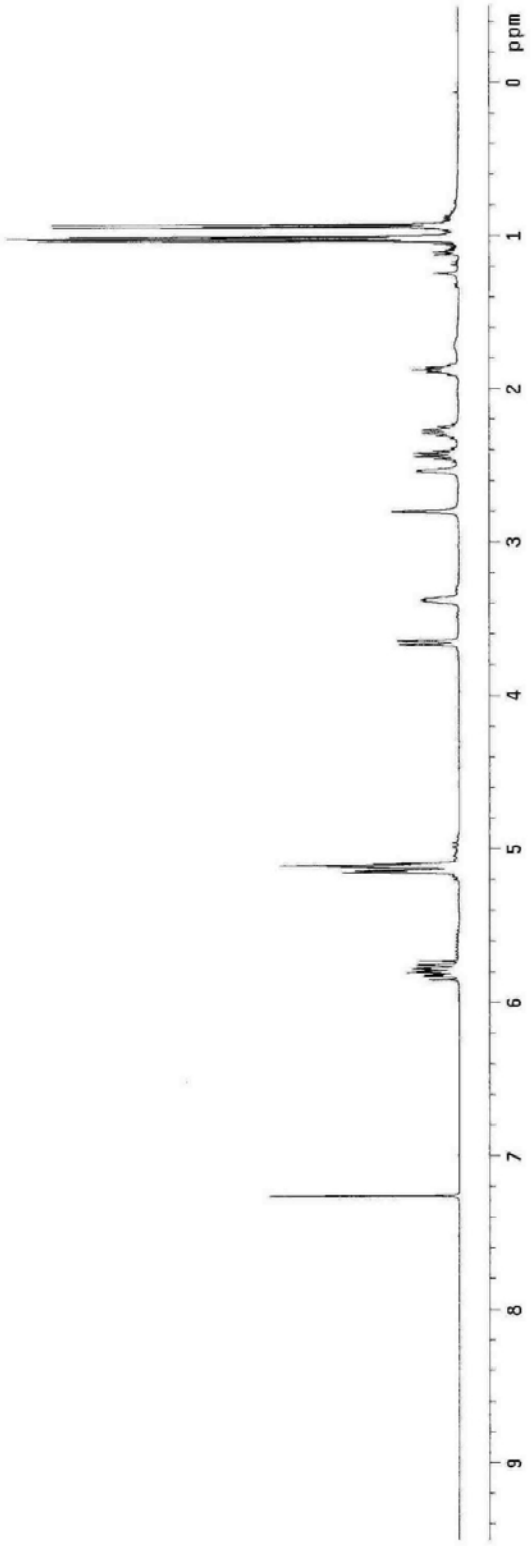
MP = 44 - 59^{o}C

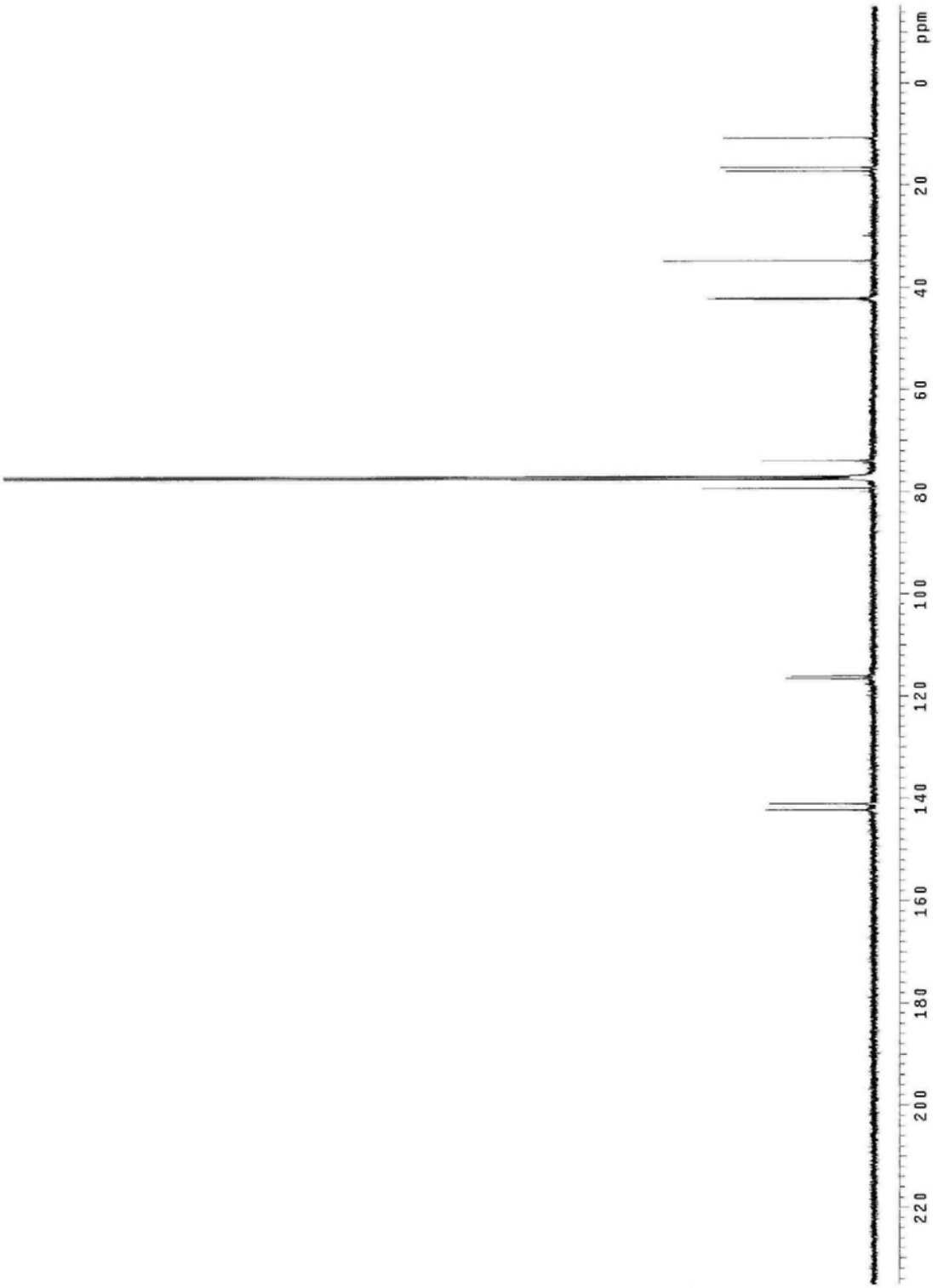
FTIR (neat): υ 3389, 2970, 2931, 1638, 1459, 1417, 1376, 1325, 1242, 1130, 1085, 1041, 994, 971, 911, 812, 720, 674.

HRMS: (CI) Calcd. for $C_{12}H_{23}O_2$ $[M+H]^+$: 199.1698, Found: 199.1696.

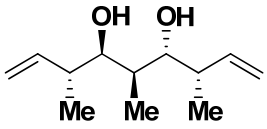


3a




ppm
0
20
40
60
80
100
120
140
160
180
200
220

(*3R,4R,5R,6R,7S*)-3,5,7-trimethylnona-1,8-diene-4,6-diol



s,a,s,a-**3b**

A solution of (*2R,3R,4R*)-3-(4-methoxybenzyloxy)-2,4-dimethylhex-5-en-1-ol(264.4 mg, 1.0 mmol, 100 mol%) in DCM (10.0 mL, 0.1 M) was cooled to 0 °C and freshly made Dess-Martin periodinane (551 mg, 1.35 mmol, 135 mol%) was added. The reaction was stirred for 30 min at 0 °C, at which point the cooling batch was removed. The reaction mixture was allowed to stir at ambient temperature for 1 hr, at which point DCM (10 mL) and saturated $NaHCO_3$ (10 mL) were added. The reaction mixture was transferred to a separatory funnel. The organic layer was separated and aqueous layer was extracted with DCM (3 × 15 mL). The combined organic extracts werewashed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was used in the next step without further purification.

To a -78 °C solution of KO^{t}Bu (168.3 mg, 1.50 mmol, 150 mol%) in THF (5 mL, 0.2 M) was added *cis*-2-butene (0.45 mL, 4.99 mmol, 500 mol%). After 5 min, ^{n}BuLi (0.93 mL,1.72M in hexanes, 1.6 mmol, 160 mol%) was added dropwise. The reaction mixture was stirred at -78 °C for 5 min and then warmed to -45 °C for 20 min, before being re-cooled to -78 °C. A solution of (+)-$(Ipc)_2$BOMe (506.1 mg, 1.6 mmol, 160 mol%) in THF (2 mL) was added dropwise, and the reaction mixture was allowed to stir for 1 hr. $BF_3.OEt_2$ (0.27 mL, 2.11 mmol, 211 mol%) was added dropwise, followed by the addition of crude (*2R,3R,4R*)-3-(4-methoxybenzyloxy)-2,4-dimethylhex-5-enal as a solution in THF (2 mL). The reaction mixture was allowed to stirat -78 °C for 4 hr. To the reaction mixture was added aqueous NaOH(1.5 mL, 3M) and H_2O_2 (0.8 mL, 30% solution). The reaction mixture was allowed to reach ambient temperature overnight, at which point aqueous HCl (1M) was added and the reaction mixture was transferred to a separatory funnel. The aqueous layer extracted with diethyl ether (3 × 20 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was used in the next step without further purification.

To a solution of the crude (*3S,4R,5R,6R,7R*)-6-(4-methoxybenzyloxy)-3,5,7-trimethylnona-1,8-dien-4-ol in DCM (10 mL, 0.1 M) was added pH 7.0 phosphate buffer (1.0 mL). The solution was cooled to 0 °C and DDQ (340 mg, 1.50 mmol, 150 mol%) was added. The reaction was stirred at 0 °C for 2 hr, at which point DCM (20 mL) and saturated $NaHCO_3$ (20 mL) were added and the reaction mixture was transferred to a separatory funnel. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:10) to give the title compound as (73.4 mg, 0.37 mmol) a colorless oil in 37% yield after three steps.

TLC (SiO_2): R_f = 0.3 (ethyl acetate:hexanes, 1:3).

^{1}H NMR(400 MHz, $CDCl_3$): δ 5.65 (ddd, *J* = 18.0, 9.6, 8.0 Hz,1H), 5.33 (dt, *J* = 17.2, 6.0 Hz,1H), 5.08-5.02 (m, 3H), 4.94(dd,*J* = 10.4, 2.0 Hz, 1H), 3.76 (d, *J* = 10.4 Hz, 1H), 3.37 (dt, *J* = 8.4, 3.6 Hz, 1H), 2.54 (br. s, 1H), 2.50-2.41 (m, 2H), 2.34-2.24 (m, 1H), 1.91-1.85 (m, 1H), 1.09 (d, *J* = 6.4 Hz, 3H),1.08 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 7.2 Hz, 3H).

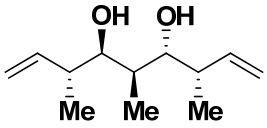
^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7, 141.6, 117.1, 114.7, 79.4, 73.5, 42.8, 42.6, 34.5, 16.4, 16.1, 10.5.

GCCyclosil-B: initial temperature 90 °C (1 min hold); final temperature 140 °C; rate = 1 °C/min; T_{major} = 45.719 min.

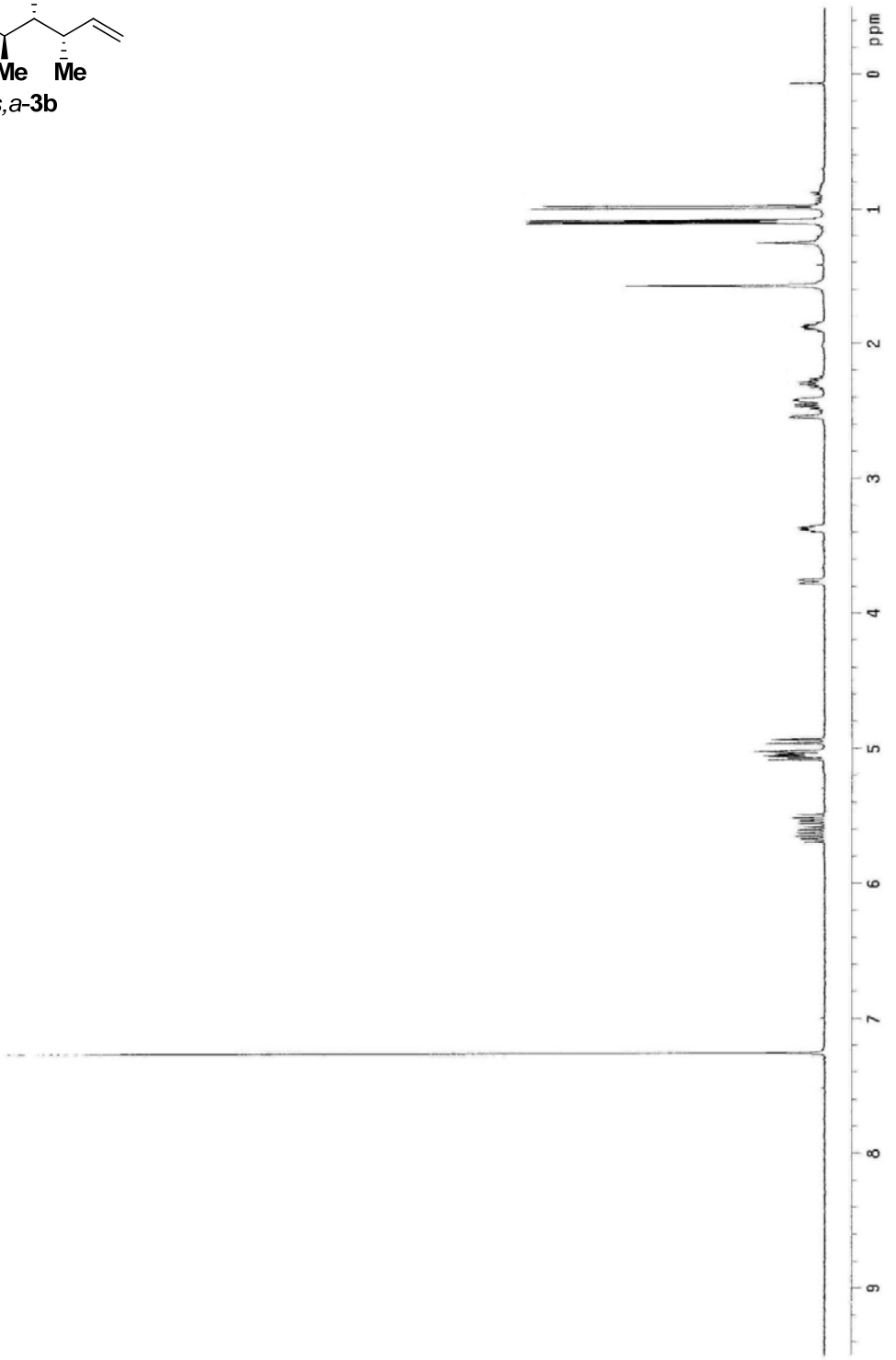
$[\alpha]_D^{25}$ = -9.6 (c = 0.3, $CHCl_3$).

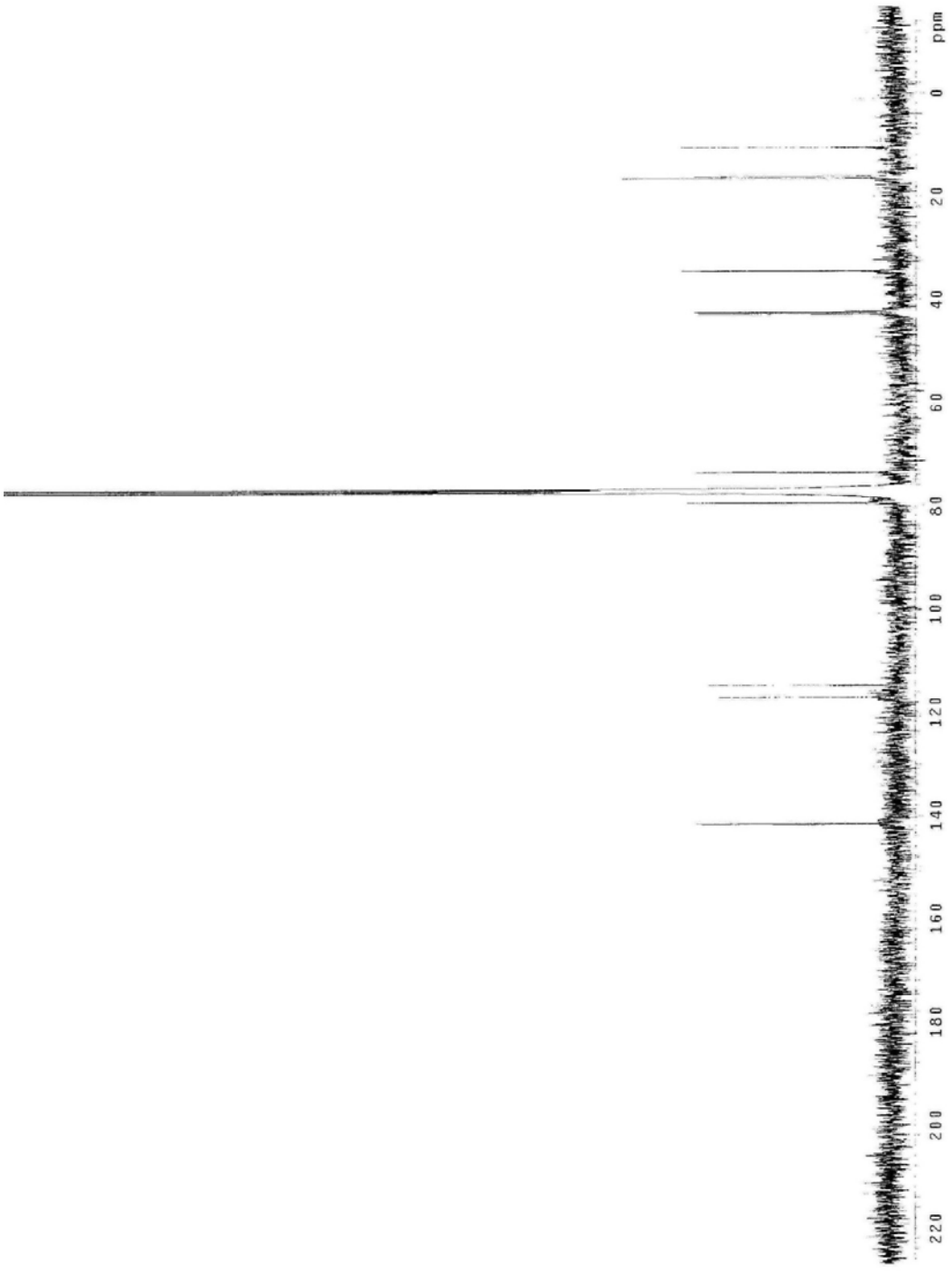
FTIR (neat): υ 3399, 2974, 2934, 1633, 1471, 1422, 1366, 1343, 1241, 1127, 1057, 1001, 968, 914, 827, 731, 676.

HRMS: (CI) Calcd. for $C_{12}H_{23}O_2$ $[M+H]^+$: 199.1698, Found: 199.1698.



s,a,s,a-**3b**




ppm
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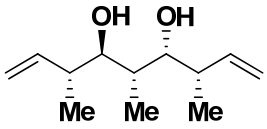
200
220

(*3R,4R,5S,6R,7S*)-3,5,7-trimethylnona-1,8-diene-4,6-diol



s,s,a,a-**3b**

A solution of (*2S,3R,4R*)-3-(4-Methoxybenzyloxy)-2,4-dimethylhex-5-en-1-ol(264.4 mg, 1.0 mmol, 100 mol%) in DCM (10.0 mL, 0.1 M) was cooled to 0 °C and freshly made Dess-Martin periodinane (551 mg, 1.35 mmol, 135 mol%) was added. The reaction was stirred for 30 min at 0 °C, at which point the cooling batch was removed. The reaction mixture was allowed to stir at ambient temperature for 1 hr, at which point DCM (10 mL) and saturated $NaHCO_3$ (10 mL) were added. The reaction mixture was transferred to a separatory funnel. The organic layer was separated and aqueous layer was extracted with DCM (3 × 15 mL). The combined organic extracts werewashed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was used in the next step without further purification.

To a -78 °C solution of KO^{t}Bu (168.3 mg, 1.50 mmol, 150 mol%) in THF (5 mL, 0.2 M) was added *cis*-2-butene (0.45 mL, 4.99 mmol, 500 mol%). After 5 min, ^{n}BuLi (0.93 mL,1.72M in hexanes, 1.6 mmol, 160 mol%) was added dropwise. The reaction was stirred at -78 °C for 5 min and then warmed to -45 °C for 20 min, before being re-cooled to -78 °C. A solution of (+)-$(Ipc)_2$BOMe (506.1 mg, 1.6 mmol, 160 mol%) in THF (2 mL) was added dropwise, and the reaction mixture was allowed to stir for 1 hr. $BF_3.OEt_2$ (0.27 mL, 2.11 mmol, 211 mol%) was added dropwise, followed by the addition of crude (*2S,3R,4R*)-3-(4-methoxybenzyloxy)-2,4-dimethylhex-5-enal as a solution in THF (2 mL). The reaction mixture was allowed to stir at -78 °C for 4 hr. To the reaction mixture was added aqueous NaOH(1.5 mL, 3M) and H_2O_2 (0.8 mL, 30% solution). The reaction mixture was allowed to reach ambient temperature overnight, at which point aqueous HCl (1M) was added and the reaction mixture was transferred to a separatory funnel. The aqueous layer extracted with diethyl ether (3 × 20 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was used in the next step without further purification.

To a solution of the crude (*3S,4R,5S,6R,7R*)-6-(4-methoxybenzyloxy)-3,5,7-trimethylnona-1,8-dien-4-ol in DCM (10 mL, 0.1 M) was added pH 7.0 phosphate buffer (1.0 mL). The solution was cooled to 0 °C and DDQ (340 mg, 1.50 mmol, 150 mol%) was added. The reaction was stirred at 0 °C for 2 hr, at which point DCM (20 mL) and saturated $NaHCO_3$ (20 mL) were added and the reaction mixture was transferred to a separatory funnel. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:10) to give the title compound (59.5 mg, 0.30 mmol) as a colorless oil in 30% yield after three steps.

(*Authentic samples 3a & ent-3a were prepared by the similar procedure described above.*)

TLC (SiO_2): R_f = 0.3 (ethyl acetate:hexanes, 1:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78 (ddd, *J* = 17.2, 9.2, 7.6 Hz, 2H), 5.73-5.62 (m, 1H), 5.20-4.96 (m, 4H), 3.67 (d, *J* = 9.6 Hz, 1H), 3.40-3.30 (m, 1H), 3.03 (d, 6.8 Hz, 1H), 2.46-2.39 (m, 1H), 2.32-2.20 (m, 2H), 1.92-1.86 (m, 1H), 1.11 (d, *J* = 7.2 Hz, 3H),1.00 (d, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H).

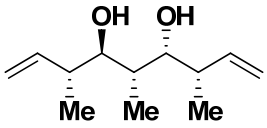
^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 140.8, 116.4, 115.8, 79.1, 73.7, 42.1, 41.8, 34.4, 16.9, 16.3, 10.5.

GCCyclosil-B: initial temperature 90 °C (1 min hold); final temperature 140 °C; rate = 1 °C/min; T_{major} = 43.702 min; T_{minor} = 48.800 min.

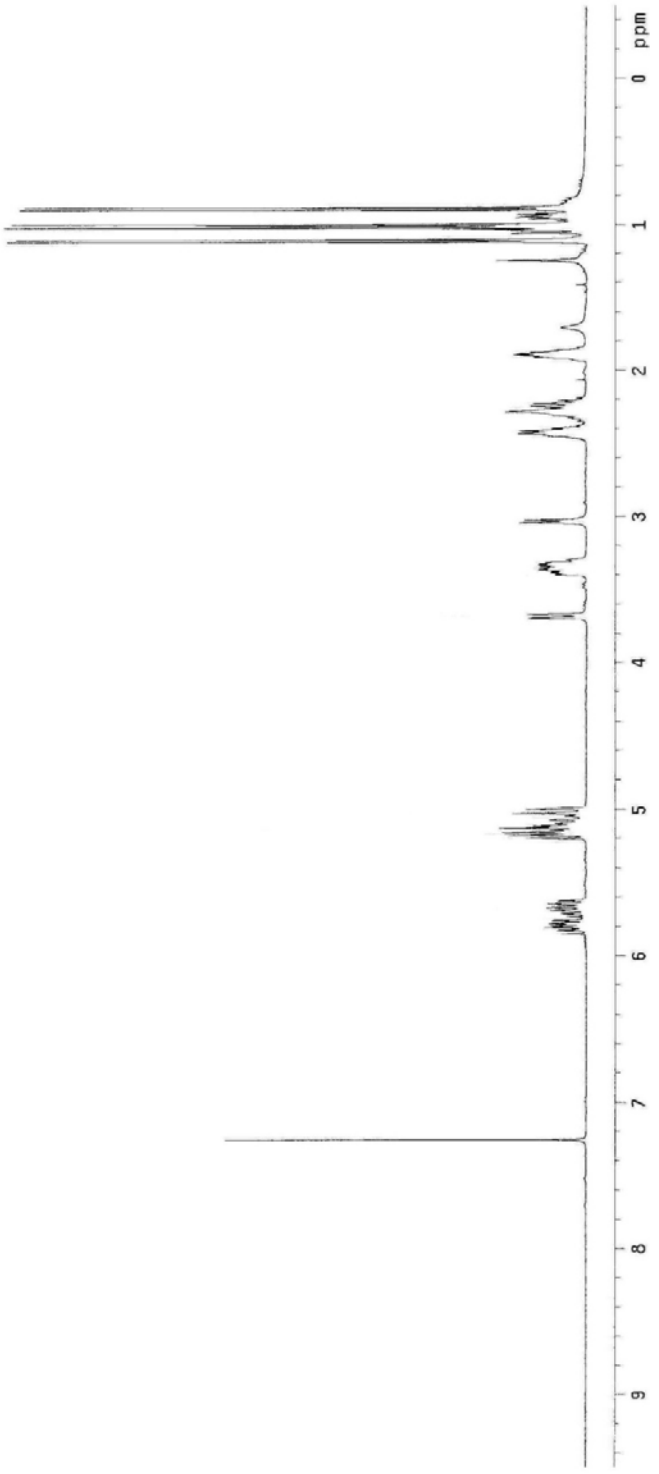
$[\alpha]_D^{25}$ = -19.6 (c = 0.31, $CHCl_3$).

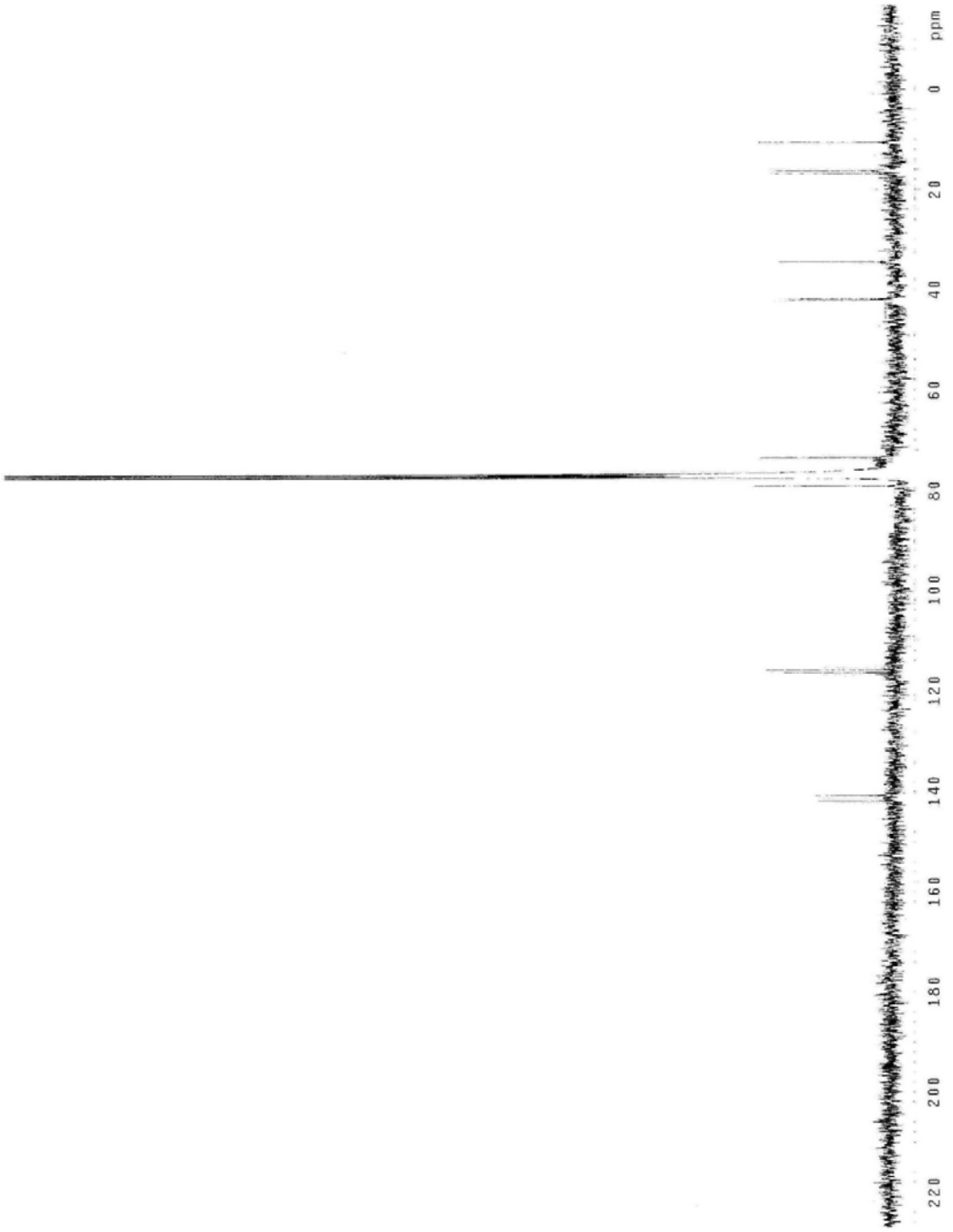
FTIR (neat): υ 3399, 2974, 2934, 1633, 1471, 1422, 1366, 1343, 1241, 1127, 1057, 1001, 968, 914, 827, 731, 676.

HRMS: (CI) Calcd. for $C_{12}H_{23}O_2$ $[M+H]^+$: 199.1698, Found: 199.1691.



s,s,a,a-**3b**

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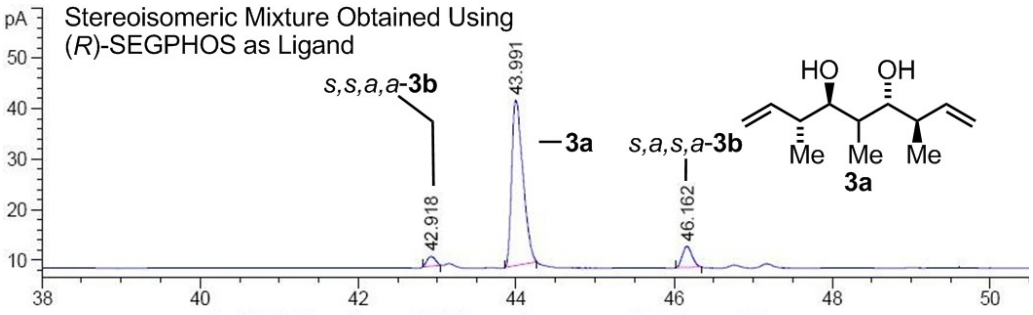
Determination of Diastereomer Ratio and Stereochemistry Confirmation-GC Comparison



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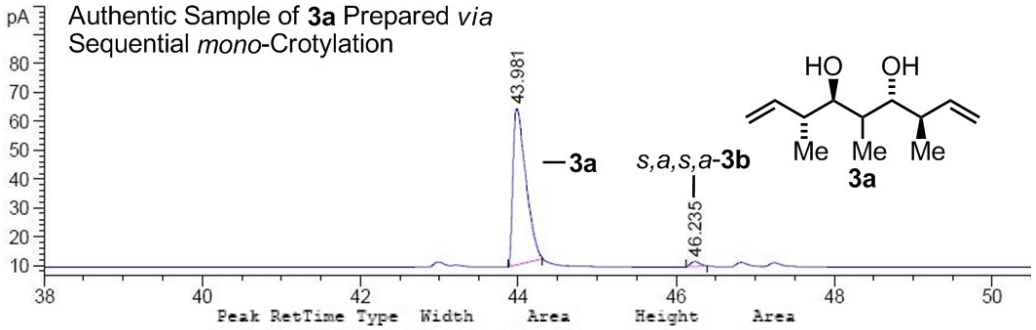
1	42.919	MM	0.1358	18.36014	2.25415	4.61468
2	43.990	MM	0.1718	340.86011	33.07572	85.67254
3	46.158	MM	0.1486	38.64366	4.33317	9.71278
Totals :				397.86390	39.66303	



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1	43.981	BB	0.1713	633.93628	52.21093	97.88732
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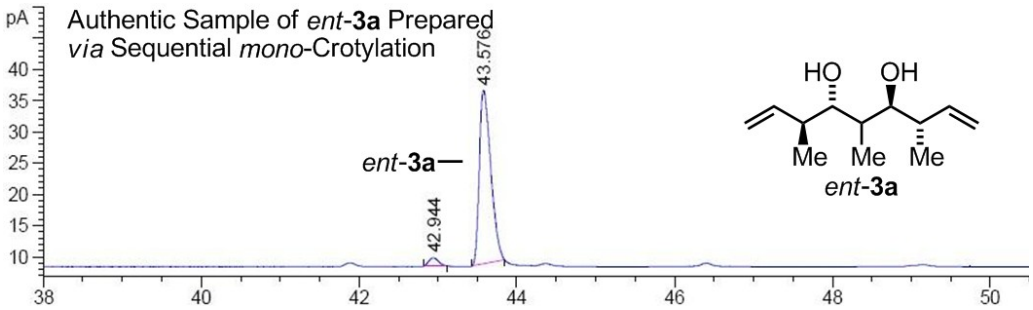
Totals :				647.61835	53.79189	



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1	42.944	BB	0.1265	12.20274	1.37771	4.01837
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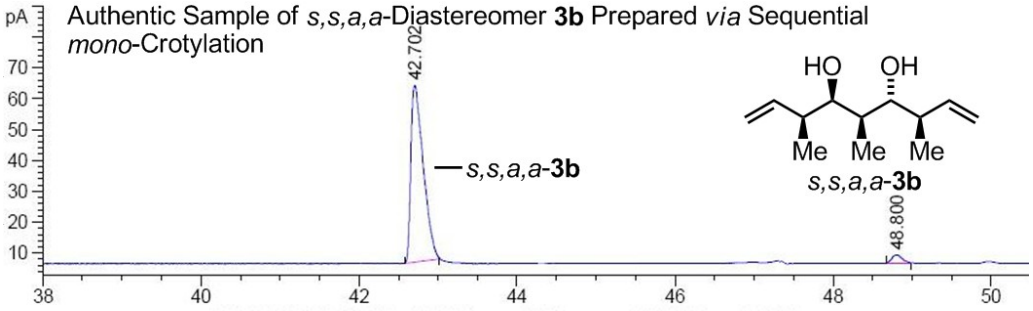

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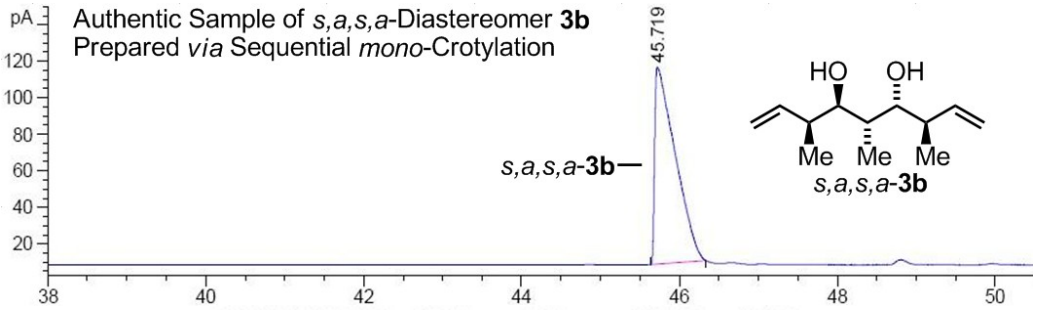
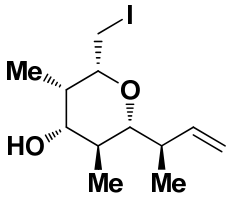
Totals :				666.87272	60.23386	



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	45.719	BB	0.2352	1987.86694	108.15513	1.000e2
Totals :				1987.86694	108.15513	

(*2R,3S,4S,5S,6R*)-2-((*R*)-but-3-en-2-yl)-6-(iodomethyl)-3,5-dimethyltetrahydro-2*H*-pyran-4-ol 4.2.4



A solution of (*3R,4R,6R,7R*)-3,5,7-trimethylnona-1,8-diene-4,6-diol (120 mg, 0.60 mmol, 100 mol%) and $NaHCO_3$ (150 mg, 1.50 mmol, 250 mol%) in acetonitrile (12.0 mL, 0.05 M) was cooled to -20 °C. To this solutionwas added iodine (381 mg, 1.80 mmol, 300 mol%) in one portion. The reaction was stirred at -20 °C for 1 hr. The reaction mixture was warmed to 0 °C and was allowed to stir at this temperature for 6 hr. Saturated aqueous $Na_2S_2O_3$was added and the reaction mixture was allowed to stiruntil the solution became colorless. The reaction mixture was transferred to a separatory funnel andthe aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:10) to give the title compound (145.9 mg, 0.45 mmol) as a colorless oil in 75% yield, ≥ 99% eeas a single diastereomer.

TLC (SiO_2): R_f = 0.5 (ethyl acetate:hexanes, 1:3).

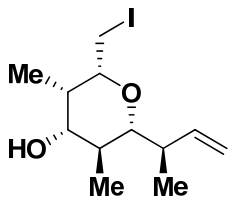
^{1}H NMR(400 MHz, $CDCl_3$): δ 5.87-5.78 (m, 1H), 5.02-4.97 (m, 2H), 3.54-3.50 (m, 1H), 3.40 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.25 (dd, *J* = 10.0, 7.6 Hz, 1H), 3.08 (dd, *J* = 10.0, 6.0 Hz, 1H), 2.88 (dd, *J* = 10.0, 2.0 Hz, 1H), 2.44-2.37 (m, 1H), 2.19-2.13 (m, 1H), 1.56-1.49 (m, 1H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 1H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 139.2, 115.2, 85.1, 78.7, 76.4, 39.9, 38.2, 34.6, 18.8, 12.2, 6.2, 4.6.

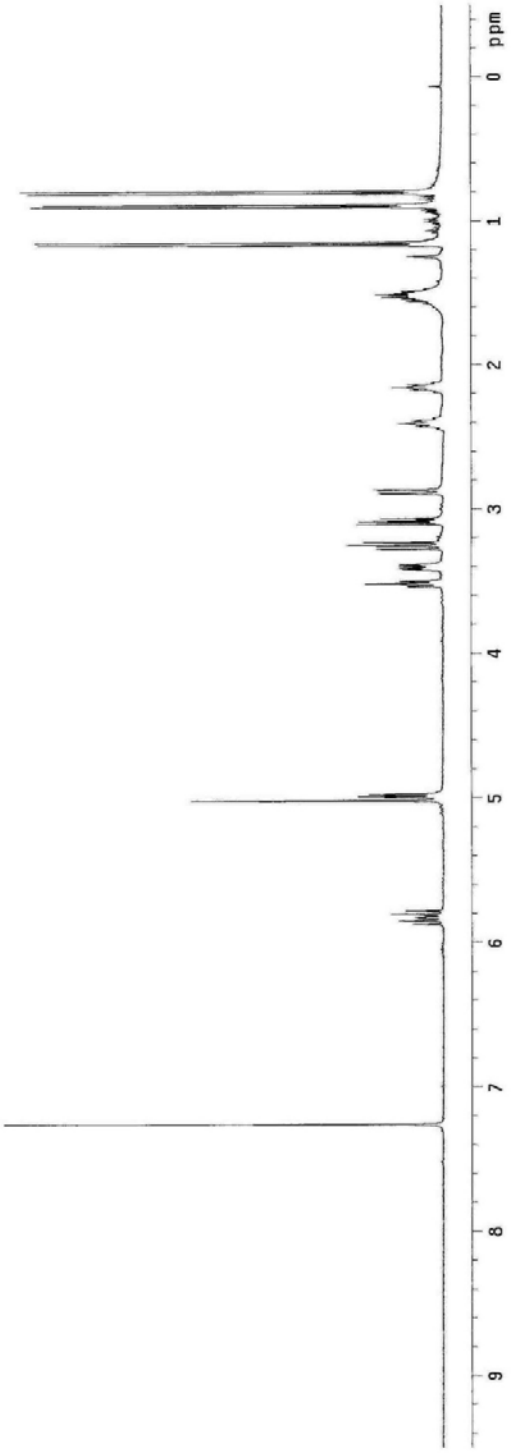
$[\alpha]_D^{25}$ = -37.1 (c = 0.57, $CHCl_3$).

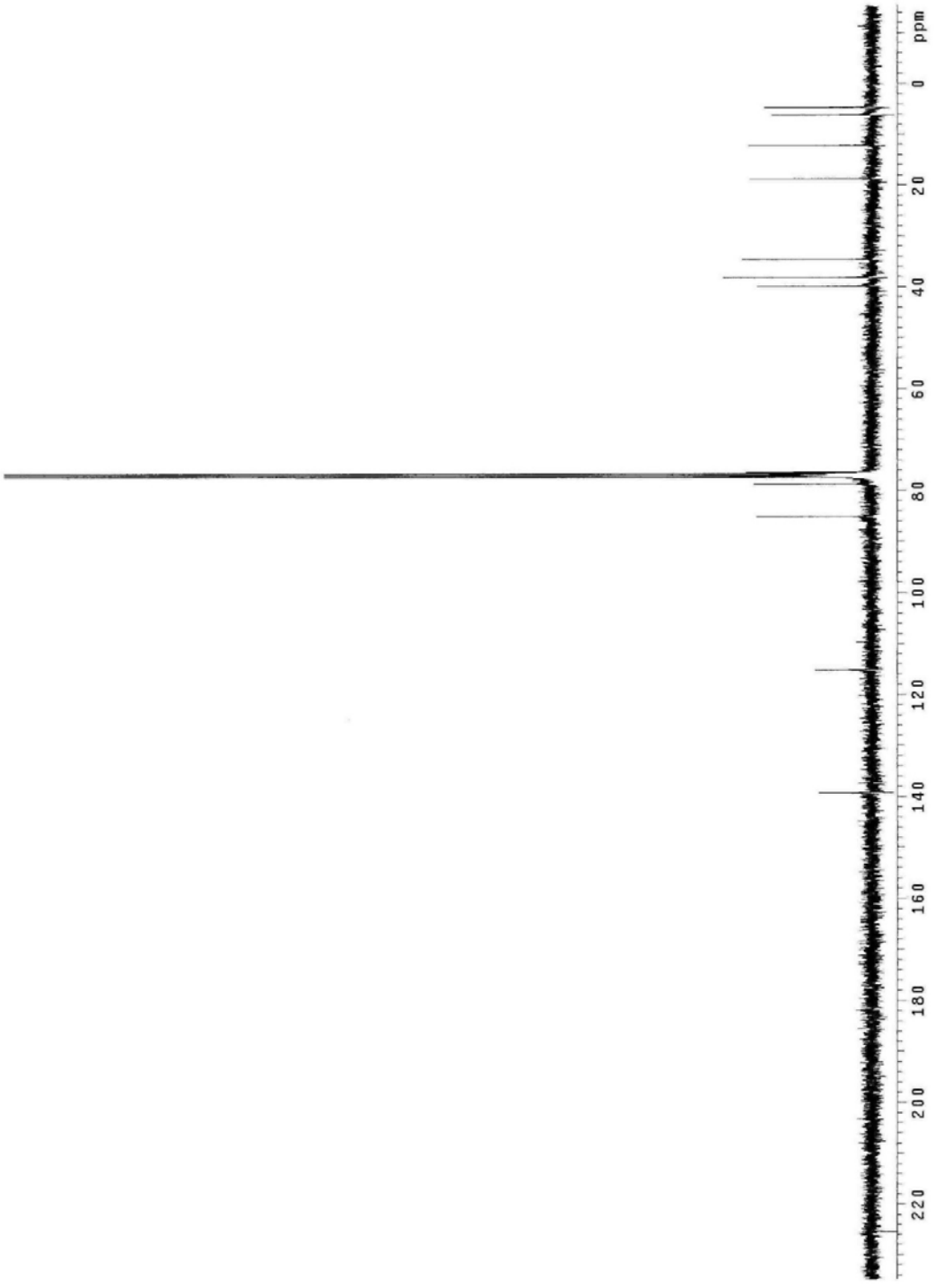
FTIR (neat): υ3350, 3075, 2963, 2925, 2853, 2362, 1640, 1458, 1416, 1372, 1336, 1300, 1271, 1242, 1175, 1091, 1070, 1043, 997, 972, 915, 876, 808, 773, 692, 668.

HRMS: (CI) Calcd. for $C_{12}H_{22}O_2I$ $[M+H]^+$: 325.0665, Found: 325.0667.



4

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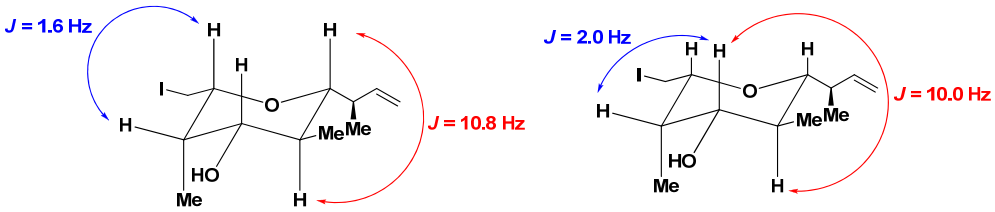
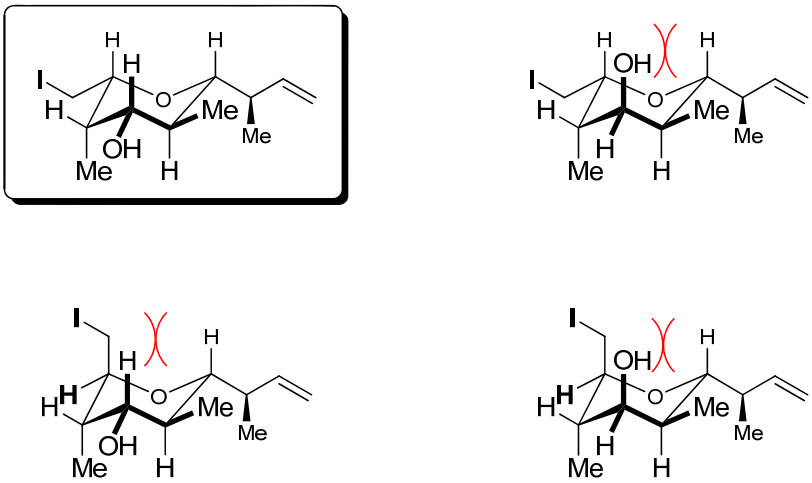
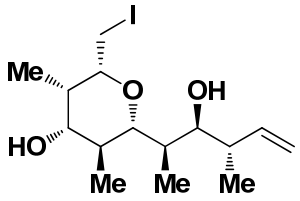
Stereochemistry Confirmation



The assignment of relative stereochemistry of the tetrahydropyran ring system was corroborated by analysis of the ^{1}H NMR coupling constants. Also, the assigned stereochemistry is consistent with known literature examples. The excellent level of stereocontrol might arise from 1,3-diaxial interactions in the transition structure en route to undesired isomer, as illustrated below.



(*2R,3S,4S,5S,6R*)-2-((*2R,3S,4S*)-3-hydroxy-4-methylhex-5-en-2-yl)-6-(iodomethyl)-3,5-dimethyltetrahydro-2*H*-pyran-4-ol 4.2.6



To a solution of (*2R,3S,4S,5S,6R*)-2-((*R*)-but-3-en-2-yl)-6-(iodomethyl)-3,5-dimethyltetrahydro-2*H*-pyran-4-ol (58 mg, 0.179 mmol, 100 mol%) in DCM:MeOH (1:1, 3.6 mL, 0.05 M) at -78 °C was added 3-5 drops of a methanolic solution of Sudan III (1.5 nM), which resulted in a light pink coloration. O_3 (2.0 $L.min^{-1}$, 15 V) was bubbled through the solutionuntil the solution became colorless. The reaction mixture was sparged with argon and Me_2S (0.1 mL) was added. The reaction mixture warmed to 0 °C and was allowed to stir overnight. The solvent was removed *in vacuo* at low temperature, and the residue was dried under high vacuum. The crude yellow oil was used in the next step without further purification.

To a solution of crude aldehyde in DCM:H_2O (1:1, 3.6 mL, 0.05 M) at ambient temperature was added Bu_4NI (6.4 mg, 0.018mmol, 10mol%) and potassium *trans*-crotyltrifluoroborate (43.4 mg, 0.267 mmol, 150 mol%). The reaction mixture was allowed to stir overnight. Brine (10 mL) was added and the reaction mixture was transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate (3 × 15 mL) and the combined organicextracts weredried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:15-1:10) to provide the title compound (50.0 mg, 0.131 mmol) as a colorless oil in 73% yield over two steps.

TLC (SiO_2): R_f = 0.3 (ethyl acetate:hexanes, 1:3).

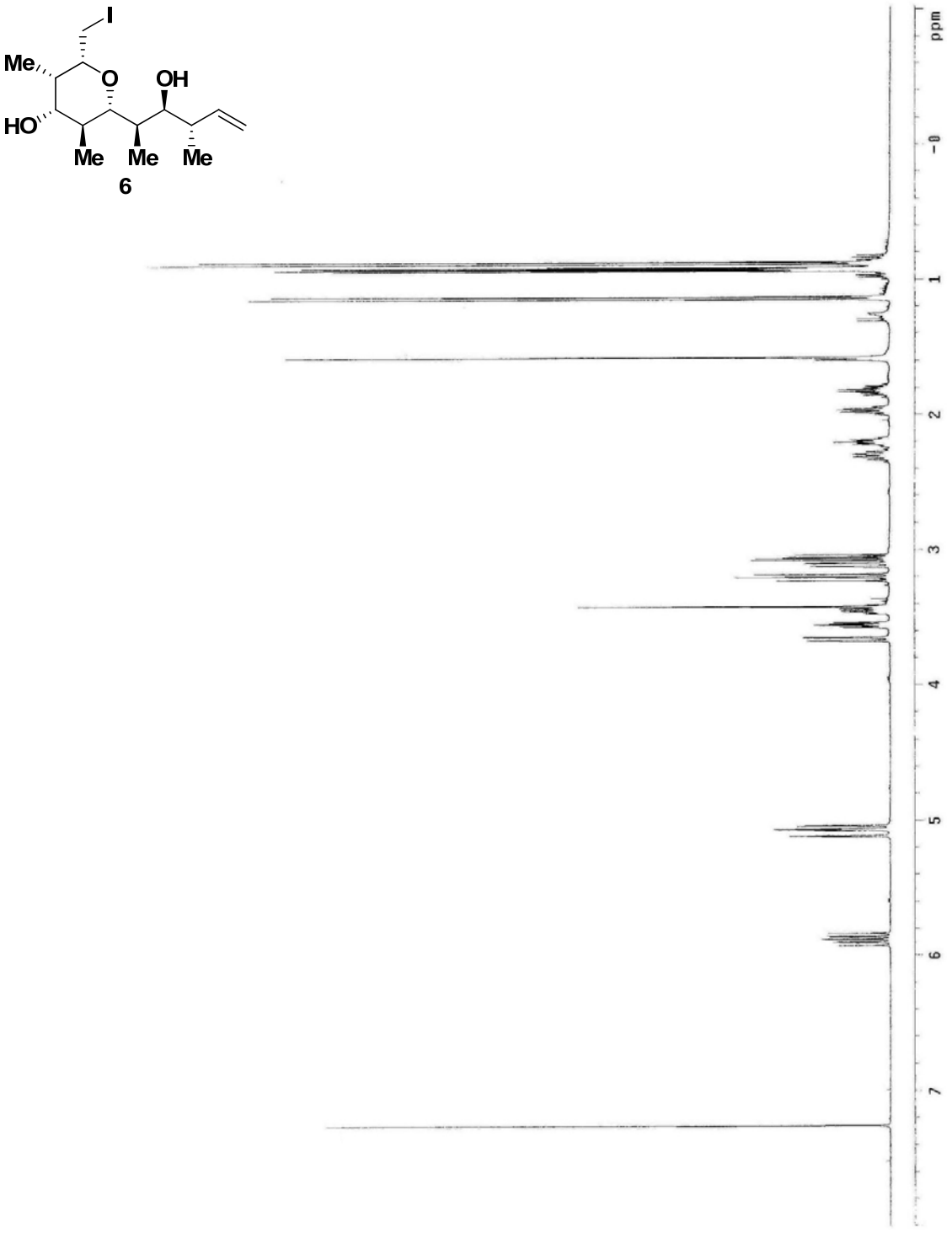
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88 (ddd, *J* = 17.6, 10.4, 8.0 Hz, 1H), 5.12-5.04 (m, 2H),3.66 (d, *J* = 9.2 Hz, 1H),3.56 (ddd, *J* = 8.8, 5.6, 2.0 Hz, 1H), 3.48-3.41 (m, 1H), 3.42 (br, 1H), 3.21 (dd, *J* = 10.4, 8.4 Hz, 1H), 3.11 (dd, *J* = 10.4, 2.0 Hz, 1H), 3.06 (dd, *J* = 10.4, 5.6 Hz, 1H), 2.30 (dq, *J* = 15.2, 6.8 Hz, 1H), 2.24-2.17 (m, 1H), 1.87 (q, *J* = 7.2 Hz, 1H), 1.87-1.77 (m, 1H), 1.14 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.1, 113.7, 88.0, 79.6, 75.7, 73.7, 41.0, 38.0, 33.5, 33.4, 16.2, 12.2, 11.2, 4.5, 4.5.

$[\alpha]_D^{25}$ = -61.9 (c = 1.00, $CHCl_3$).

FTIR (neat): υ3371, 3080, 2961, 2915, 2872, 2350, 1635, 1444, 1426, 1350, 1292, 1242, 1165, 1077, 1070, 1033, 997, 972, 915, 816, 692, 673.

HRMS: (CI) Calcd. for $C_{15}H_{28}O_3I$ $[M+H]^+$: 383.1084, Found: 383.1083.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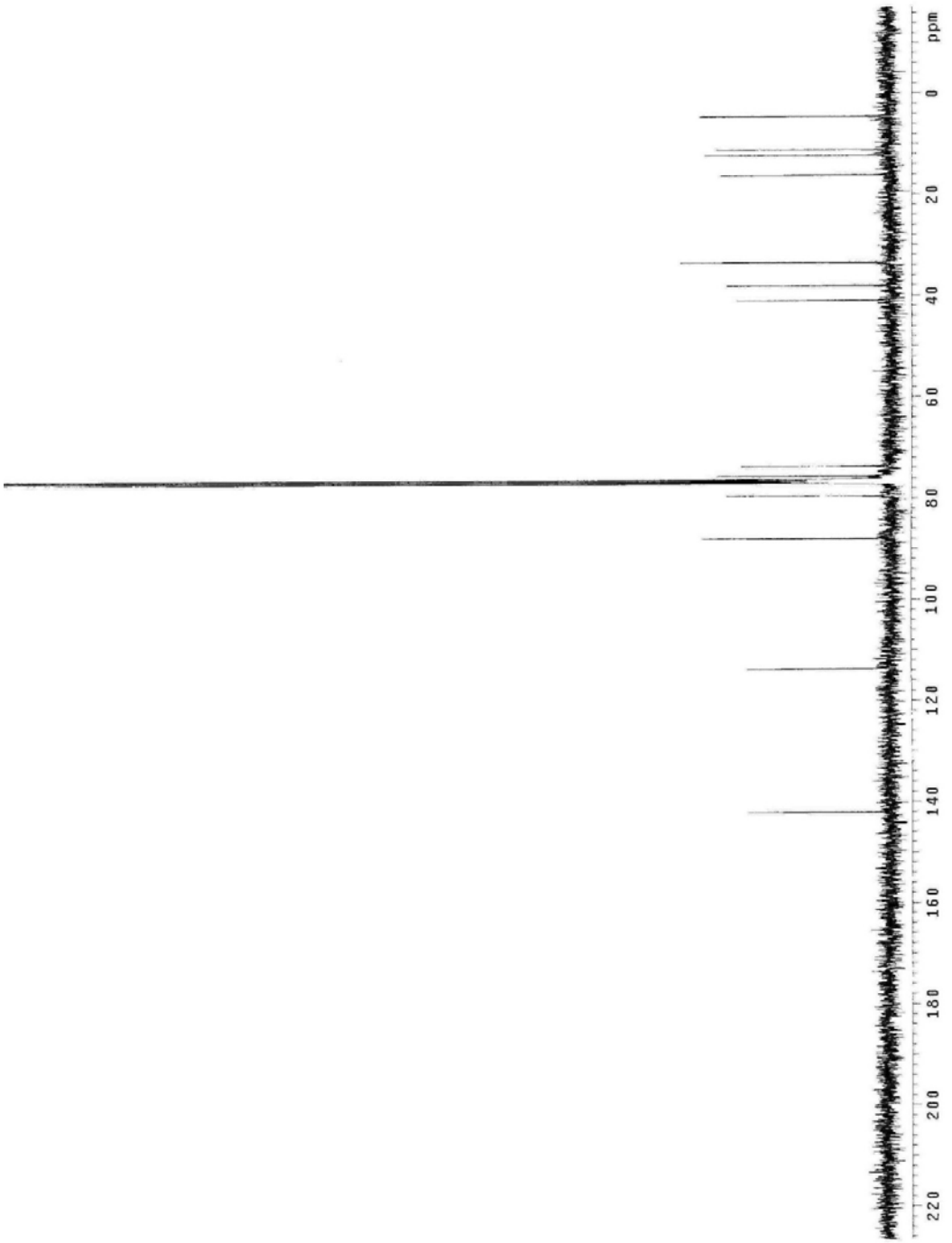
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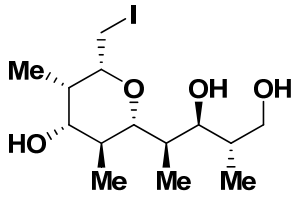
(*2S,3S,4R*)-4-((*2R,3S,4S,5S,6R*)-4-Hydroxy-6-(iodomethyl)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)-2-methylpentane-1,3-diol 4.2.7



To a solution of (*2R,3S,4S,5S,6R*)-2-((*2R,3S,4S*)-3-hydroxy-4-methylhex-5-en-2-yl)-6-(iodomethyl)-3,5-dimethyltetrahydro-2*H*-pyran-4-ol (76.4 mg, 0.20 mmol, 100 mol%) in DCM:MeOH (1:1, 4 mL, 0.05 M) was added 3-5 drops of a methanolic solution of Sudan III (1.5 nM), which resulted in a light pink coloration. O_3 (2.0 $L.min^{-1}$, 15 V) was bubbled through the solution until the solution became colorless. The reaction mixture was sparged with argon and $NaBH_4$ (75.6 mg, 2.0 mmol, 1000 mol%) was added. The reaction mixture warmed to ambient temperature and was allowed to stir overnight. Brine (60 mL) was added and the reaction mixture was transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate (3 × 30 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2: ethyl ether:DCM, 1:5-1:1) to provide the title compound (64.5 mg, 0.167 mmol) as a colorless oil in 84% yield.

TLC (SiO_2): R_f = 0.2 (ether:DCM, 1:2).

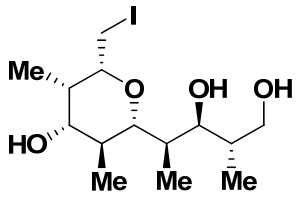
^{1}H NMR (400 MHz, DMSO): δ 3.81 (dd, *J* = 10.4, 1.6 Hz, 1H), 3.69-3.57 (m, 2H), 3.49-3.41 (m, 2H), 3.23 (dd, *J* = 10.4, 8.0 Hz, 1H), 3.09 (dd, *J* = 10.4, 1.6 Hz, 1H), 3.03 (dd, *J* = 10.4, 6.0 Hz, 1H), 2.30-2.21 (m, 1H), 2.03-1.94 (m, 1H), 1.71-1.54 (m, 2H), 1.22 (d, *J* = 7.2 Hz, 3H), 0.97 (d, *J* = 8.0 Hz, 3H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.68 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, DMSO): δ 90.7, 80.0, 75.3, 73.9, 61.6, 37.9, 35.0, 33.8, 32.9, 16.3, 13.4, 9.9, 5.2, 5.2.

$[\alpha]_D^{26}$ = +37.7 (c = 1.00, $CHCl_3$).

FTIR (neat): υ 3630, 2988, 2923, 2892, 2369, 1624, 1432, 1429, 1334, 1283, 1174, 1107, 1070, 933, 928, 815, 700, 679.

HRMS: (CI) Calcd. for $C_{14}H_{27}O_4I$ $[M]^+$: 386.0955, Found: 386.0960.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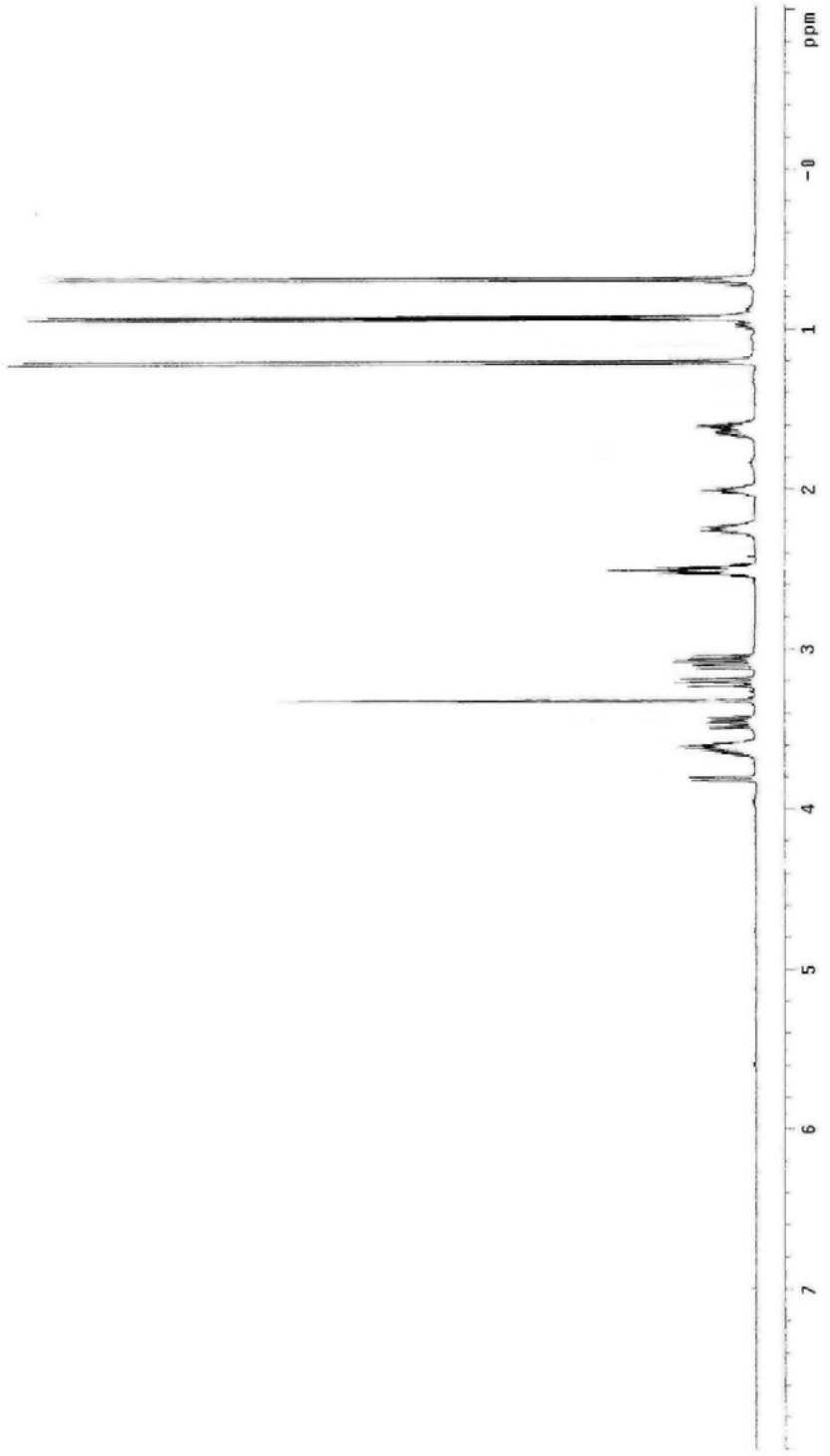
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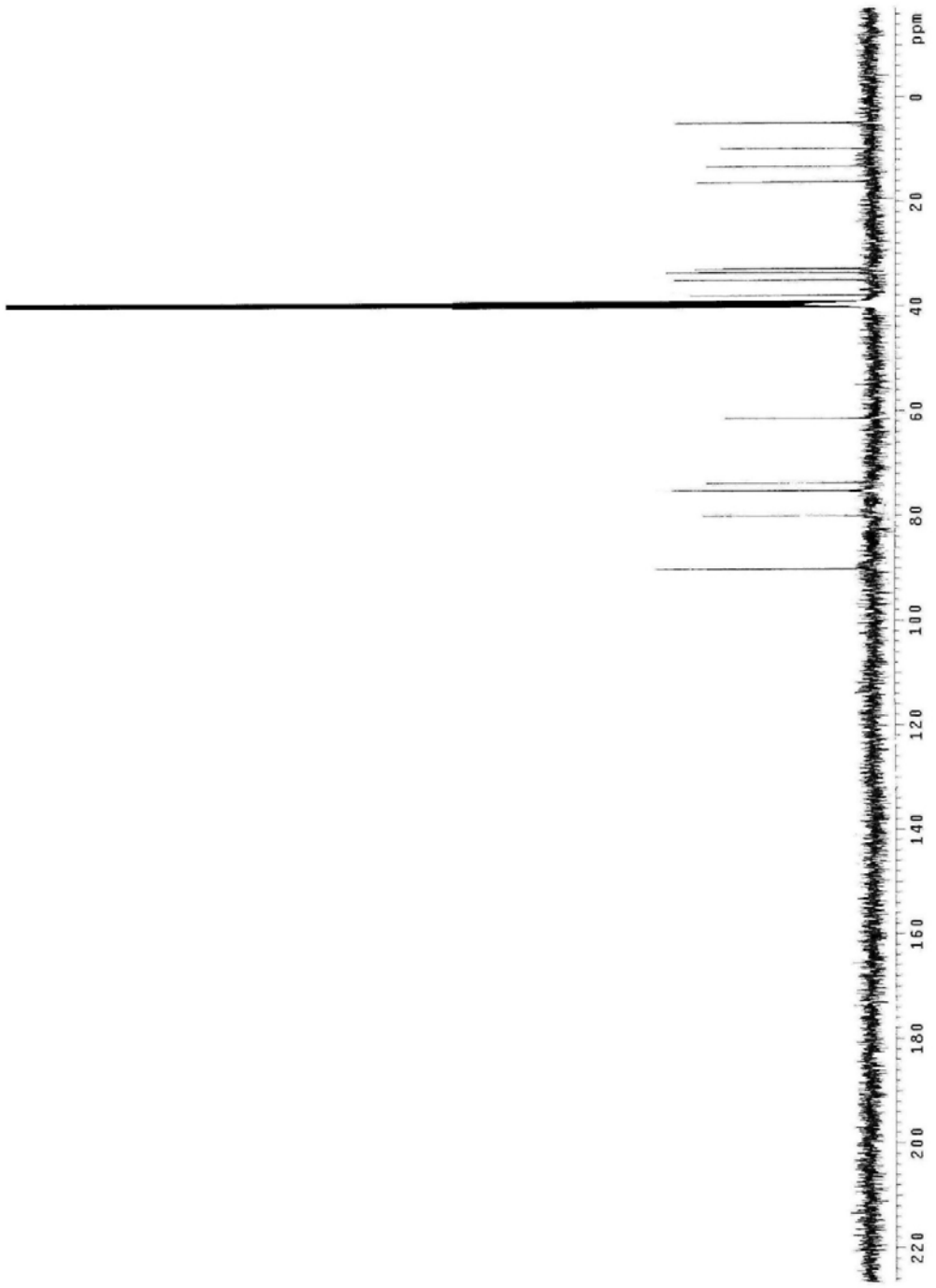
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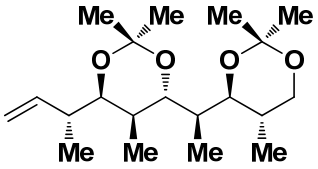
(*4R,5S,6S*)-4-((*R*)-But-3-en-2-yl)-2,2,5-trimethyl-6-((*R*)-1-((*4S,5S*)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethyl)-1,3-dioxane 4.2.9



To a solution of (*2S,3S,4R*)-4-((*2R,3S,4S,5S,6R*)-4-hydroxy-6-(iodomethyl)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)-2-methylpentane-1,3-diol (33.0 mg, 0.085 mmol, 100 mol%) in EtOH (0.85 mL, 0.1 M) was added activated Zn (83.5 mg, 1.28 mmol, 1500 mol%) and NH_4Cl (45.5 mg, 0.85 mmol, 1000 mol%). The reaction mixture was allowed to stir overnight under reflux. Then the reaction mixture was filtered through a short plug of silica gel with the aid of ethyl acetate. The resulting liquor was concentrated under reduced pressure and dried under high vacuum. The crude yellow oil was used in the next step without further purification.

To a solution of crude tetraol in acetone (1.24 mL, 0.05 M) was added 2-methoxyprop-1-ene (44.7 mg, 0.62 mmol, 1000 mol%) and PPTS (0.5 mg, 0.01 mmol, 20 mmol%). The reaction mixture was stirred under ambient temperature and monitored by TLC. After 30 mins, saturated $NaHCO_3$ (5 mL) was added and the reaction mixture was transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate (3 × 15 mL) and the combined organicextracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:100) to give the title compound (20.1 mg, 0.059 mmol) as a colorless oil in 69% yield over two steps.

TLC (SiO_2): R_f = 0.4 (ethyl acetate:hexanes, 2:98).

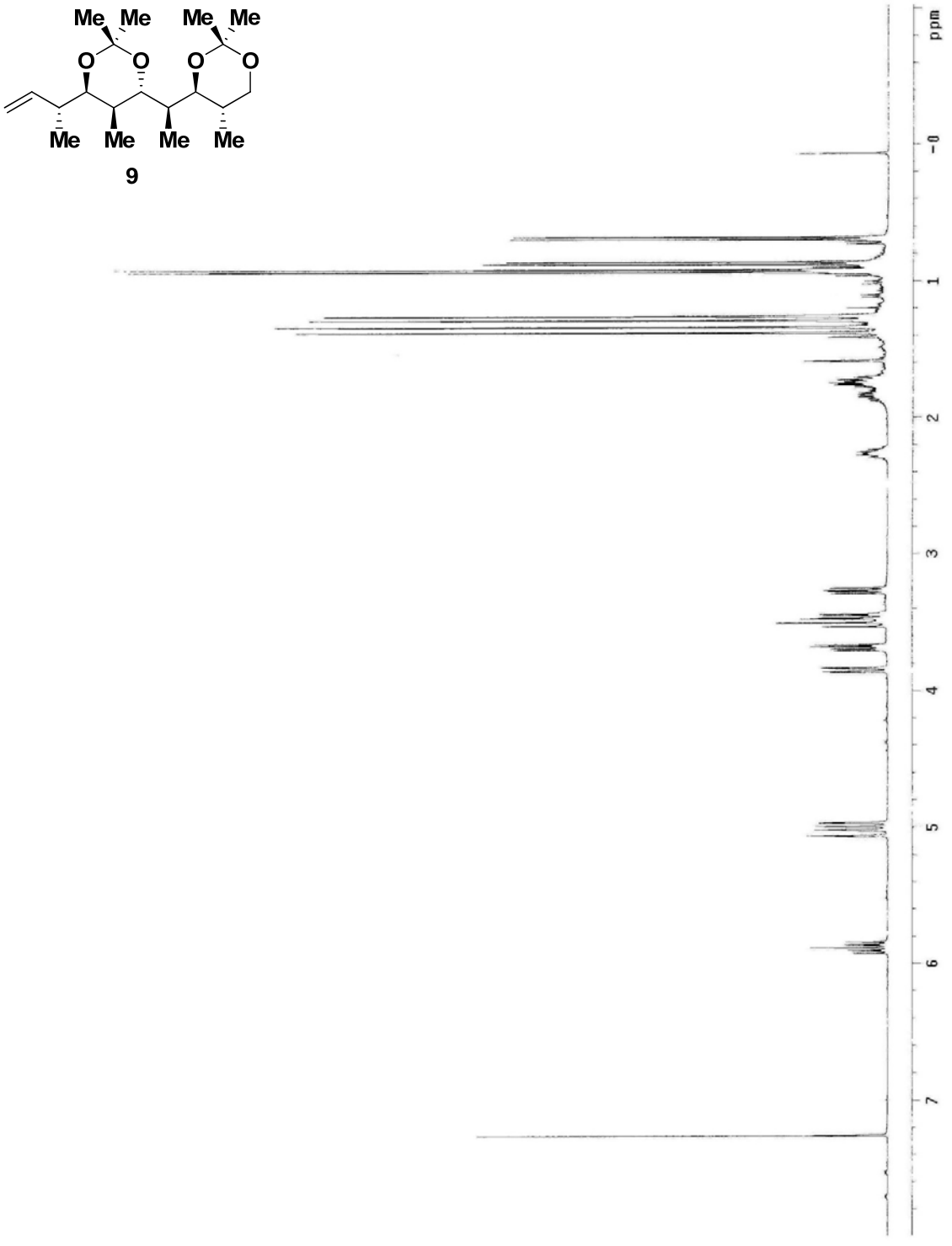
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88 (ddd, *J* = 17.2, 10.4, 6.4 Hz, 1H), 5.07-4.97 (m, 2H), 3.85 (dd, *J* = 10.8, 2.0 Hz, 1H),3.68 (dd, *J* = 10.8, 5.2 Hz, 1H),3.51 (t, *J* = 11.2 Hz, 1H), 3.46 (dd, *J* = 10.4, 3.6 Hz, 1H), 3.27 (dd, *J* = 9.2, 6.4 Hz, 1H), 2.31-2.22 (m, 1H), 1.88-1.70 (m, 3H), 1.38 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H), 1.26 (s, 3H), 0.92 (d, *J* = 6.4 Hz, 6H), 0.87 (d, *J* = 7.2 Hz, 3H), 0.69 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ142.4, 113.3, 100.3, 98.0, 74.1, 73.2, 72.8, 66.6, 39.2, 36.8, 36.7, 30.4, 29.8, 25.7, 23.5, 19.0, 15.6, 12.9, 12.1, 7.7.

$[\alpha]_D^{25}$ = +0.4 (c = 1.17, $CHCl_3$).

FTIR (neat): υ3073, 2978, 2935, 1842, 1640, 1431, 1378, 1359, 1171, 1119, 1111, 1013, 1000, 979,833, 851, 637.

HRMS: (CI) Calcd. for $C_{20}H_{37}O_4$ $[M+H]^+$: 341.2693, Found: 341.2700.



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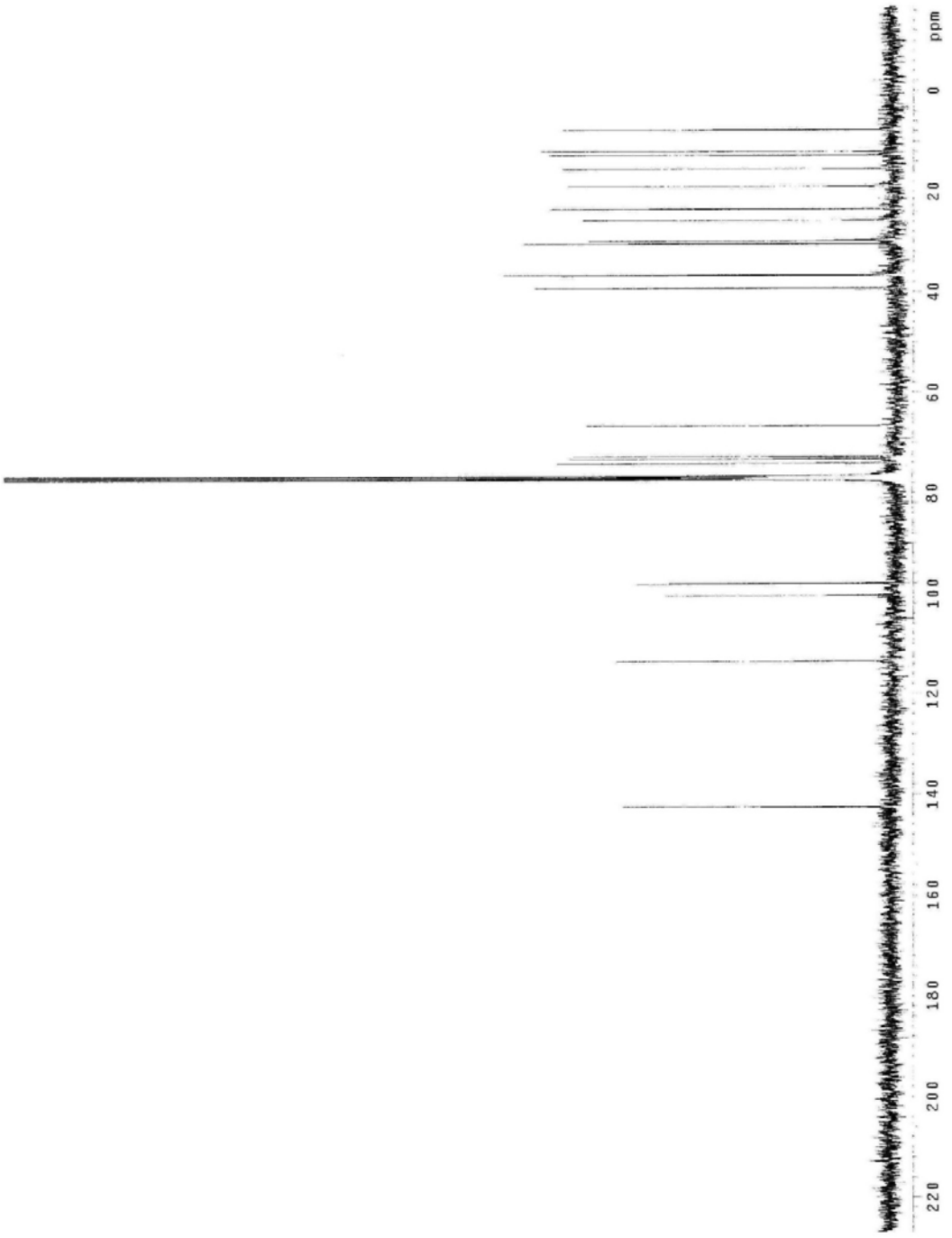
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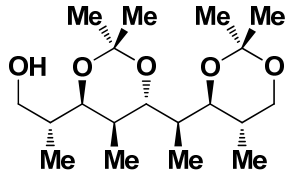
(*R*)-2-((*4R,5S,6S*)-2,2,5-Trimethyl-6-((*R*)-1-((*4S,5S*)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethyl)-1,3-dioxan-4-yl)propan-1-ol (Rifamycin S: C19-C27 Fragment) 4.2.10



To a solution of (*4R,5S,6S*)-4-((*R*)-but-3-en-2-yl)-2,2,5-trimethyl-6-((*R*)-1-((*4S,5S*)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethyl)-1,3-dioxane (20.1 mg, 0.059 mmol, 100 mol%) in DCM:MeOH (1:1, 1.2 mL, 0.05 M) was added 3-5 drops of a methanolic solution of Sudan III (1.5 nM), which resulted in a light pink coloration. O_3 (2.0 L.min^{-1}, 15 V) was bubbled through the solution until the color changed from pink to colorless. The reaction mixture was purged with argon, and $NaBH_4$ (22.3 mg, 0.59 mmol, 1000 mol%) was added. The reaction warmed to ambient temperature and was allowed to stir overnight. Brine (10 mL) was added and the reaction mixture was transferred to a separatory funnel. The aqueous layer was extracted with DCM (3 × 15 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:10) gave the title compound (19.5 mg, 0.057 mmol) as a colorless oil in 96% yield.

TLC (SiO_2): R_f = 0.3 (ethyl acetate:hexanes, 1:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (dd, *J* = 10.4, 1.6 Hz, 1H), 3.71-3.66 (m, 2H), 3.59-3.48 (m, 3H), 3.30-3.28 (m, 2H),1.95-1.81 (m, 2H), 1.77-1.70 (m, 2H), 1.38 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 7.2 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H), 0.69 (d, *J* = 6.8 Hz, 3H).

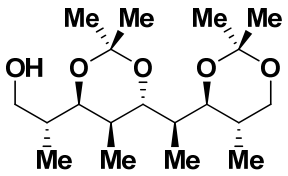
^{13}C NMR(100 MHz, $CDCl_3$): δ100.5, 98.0, 76.2, 74.0, 72.7, 69.4, 66.6, 39.2, 36.7, 34.8, 30.3, 29.8, 26.1, 23.4, 19.0, 13.0, 12.6, 12.1, 7.7.

$[\alpha]_D^{25}$ = -5.2 (c = 0.75, $CHCl_3$).

FTIR (neat): υ3473, 2999, 2945, 2879, 1454, 1441, 1416, 1381, 1290, 1223, 1164, 1145, 1077,994, 973, 902, 877.

HRMS: (CI) Calcd. for $C_{19}H_{35}O_5$ $[M-H]^+$: 343.2485, Found: 343.2489.

The spectroscopic properties of this compound and corrosponding acetate were consistent with the data available in the literature.



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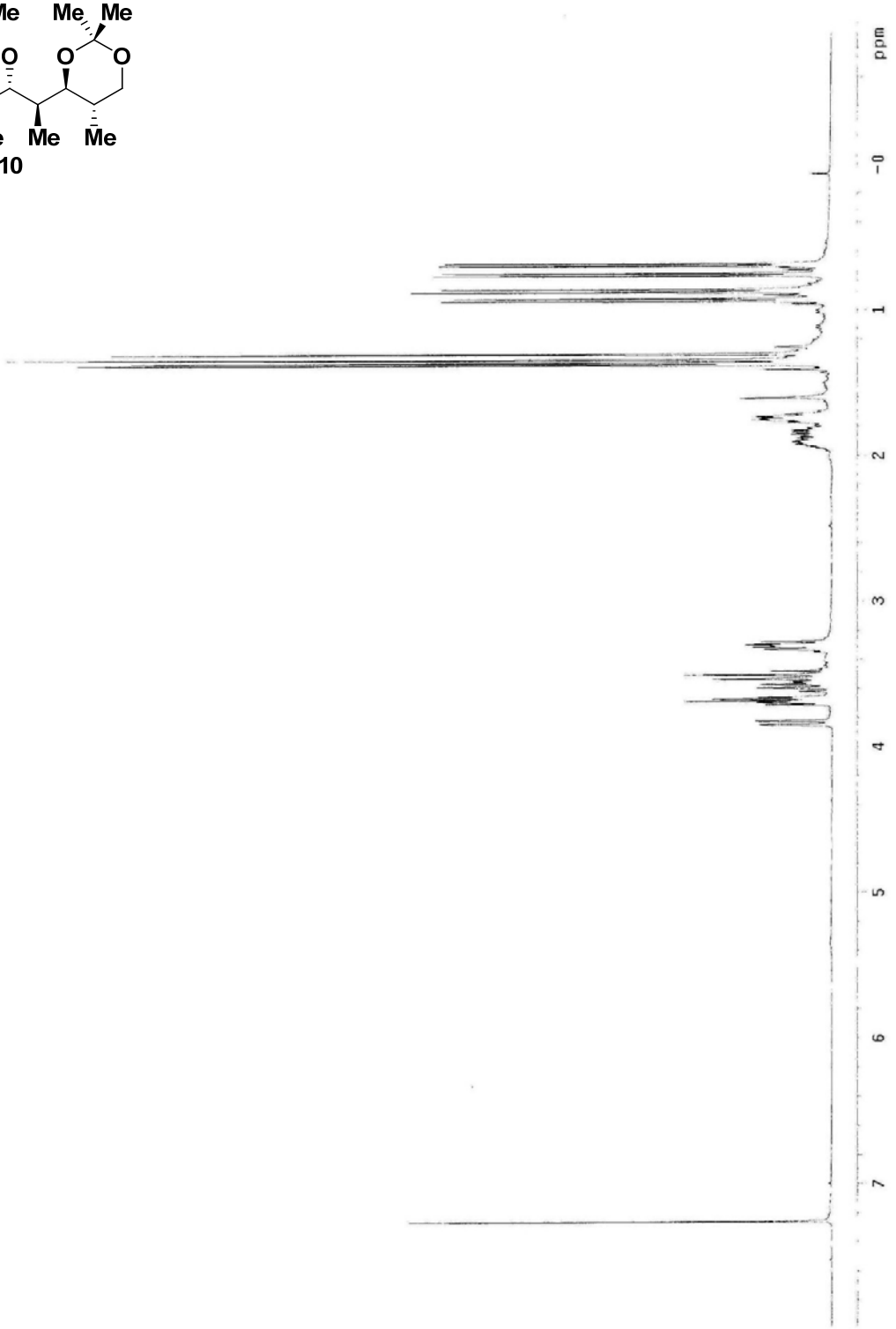


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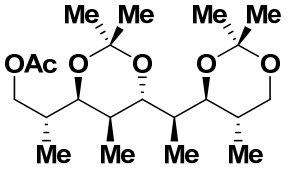
(*R*)-2-((*4R,5S,6S*)-2,2,5-Trimethyl-6-((*R*)-1-((*4S,5S*)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethyl)-1,3-dioxan-4-yl)propyl acetate



To a solution of (*R*)-2-((*4R,5S,6S*)-2,2,5-trimethyl-6-((*R*)-1-((*4S,5S*)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethyl)-1,3-dioxan-4-yl)propan-1-ol(19.5 mg, 0.057 mmol, 100 mol%) in DCM (1.2 mL, 0.05 M) was added triethylamine (17.3 mg, 0.171 mmol, 300 mol%) and acetic anhydride (11.6 mg, 0.114, 200 mol%). The reaction mixture was stirred for 3 hr under ambient temperature. Saturated $NaHCO_3$ (5 mL) was added and the reaction misture was transferred to a separatory funnel. The aqueous layer was extracted with DCM (3 × 5 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:15) gave the title compound (19.8 mg, 0.051 mmol) as a colorless oil in 90% yield.

TLC (SiO_2): R_f = 0.6 (ethyl acetate:hexanes, 1:4).

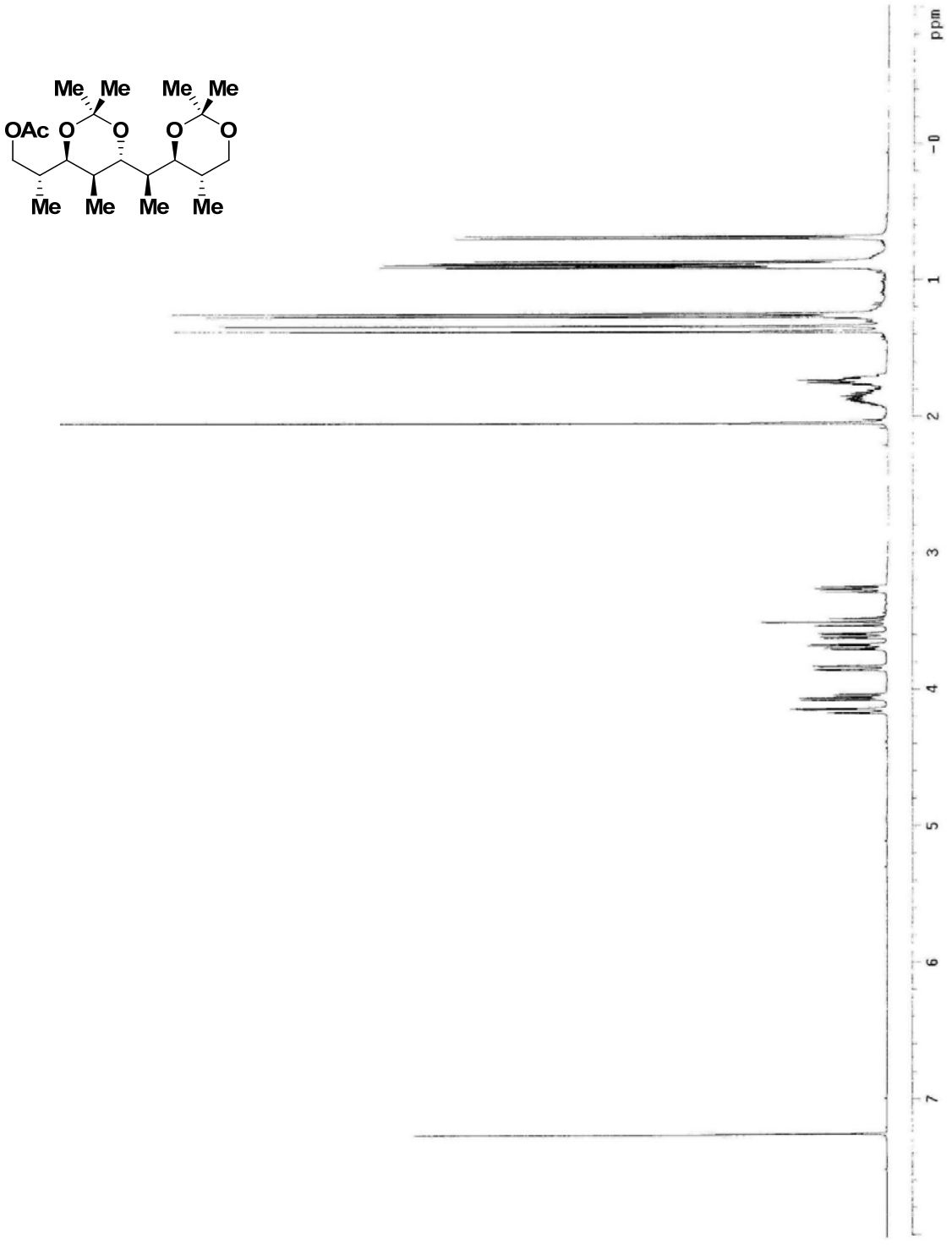
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.16 (dd, *J* = 10.4, 2.8 Hz, 1H), 4.06 (dd, *J* = 10.4, 6.0 Hz, 1H), 3.84 (dd, *J* = 10.4, 2.0 Hz, 1H), 3.68 (dd, *J* = 11.6, 5.2 Hz, 1H),3.61 (dd, *J* = 10.0, 3.6 Hz, 1H), 3.51 (t, *J* = 11.2 Hz, 1H), 3.27 (dd, *J* = 9.6, 6.4 Hz, 1H),2.05 (s,3H),1.93-1.80 (m, 2H), 1.79-1.69 (m, 2H), 1.38 (s, 3H), 1.34 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.69 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ171.3, 100.4, 98.0, 74.1, 72.7, 69.7, 66.6, 66.6, 39.2, 36.4, 32.5, 30.4, 29.8, 25.6, 23.4, 21.0, 19.0, 12.9, 12.7, 12.1, 7.8.

$[\alpha]_D^{25}$ = +16.2 (c = 1.07, $CHCl_3$).

FTIR (neat): υ3413, 3094, 2955, 2833, 2357, 1400, 1372, 1334, 1300, 1271, 1205, 1175, 1025, 999, 987, 692, 668.

HRMS: (CI) Calcd. for $C_{21}H_{38}O_6$ $[M]^+$: 386.2669, Found: 386.2669.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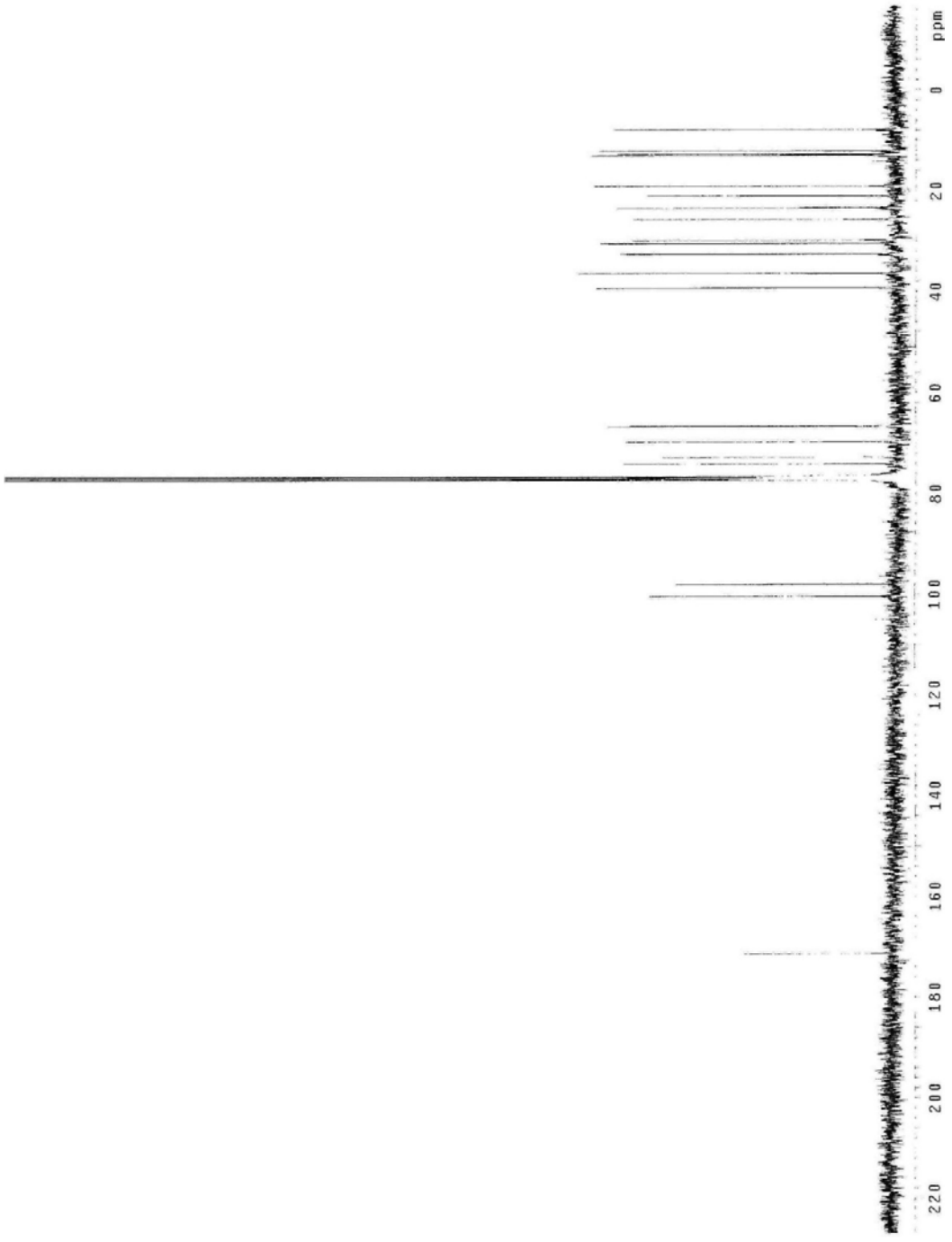
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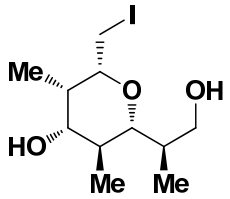
(*2R,3S,4S,5S,6R*)-2-((*R*)-1-hydroxypropan-2-yl)-6-(iodomethyl)-3,5-dimethyltetrahydro-2*H*-pyran-4-ol 4.2.11



A solution of (*2R,3S,4S,5S,6R*)-2-((*R*)-but-3-en-2-yl)-6-(iodomethyl)-3,5-dimethyltetrahydro-2*H*-pyran-4-ol (162.1 mg, 0.50 mmol, 100 mol%) in DCM:MeOH (1:1, 10 mL, 0.05 M) was added 3-5 drops of a methanolic solution of Sudan III (1.5 nM), which resulted in a light pink coloration. O_3 (2.0 $L.min^{-1}$, 15 V) was bubbled through the solution until the color changed from pink to colorless. The reaction mixture was purged with argon, and $NaBH_4$ (189.2 mg, 5.0 mmol, 1000 mol%) was added. The reaction warmed to ambient temperature and was allowed to stir overnight. Brine (30 mL) was added and the reaction mixture was transferred to a separatory funnel. The aqueous layer was extracted with DCM (3 × 15 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:1) gave the title compound (131.3 mg, 0.40 mmol) as a colorless oil in 80% yield.

TLC (SiO_2): R_f = 0.5 (ethyl acetate:hexanes, 1:1).

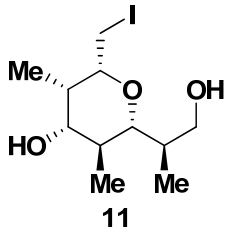
^{1}H NMR(400 MHz, $CDCl_3$): δ 3.90 (dd, *J* = 10.8, 2.8 Hz, 1H), 3.58-3.51 (m, 2H), 3.44-3.40 (m, 1H), 3.24 (dd, *J* = 10.0, 8.0 Hz, 1H), 3.10-3.05 (m, 2H), 2.45 (d, *J* = 7.6 Hz, 1H), 2.23-2.17 (m, 1H), 1.93-1.86 (m, 1H), 1.79-1.72 (m, 1H), 1.67 (br. s, 1H), 1.22 (d, *J* = 7.2 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 87.3, 79.6, 76.2, 63.7, 38.2, 34.9, 34.7, 15.9, 12.8, 5.3, 4.8.

$[\alpha]_D^{27}$ = +62 (c = 0.6, CH_2Cl_2).

FTIR (neat): υ 3352, 2965, 2927, 1458, 1415, 1389, 1266, 1180, 1131, 1097, 1059, 1038, 1009, 983, 967, 937, 890, 803, 736, 697.

HRMS: (CI) Calcd. for $C_{11}H_{22}O_3I$ $[M+H]^+$: 329.0614, Found: 329.0610.



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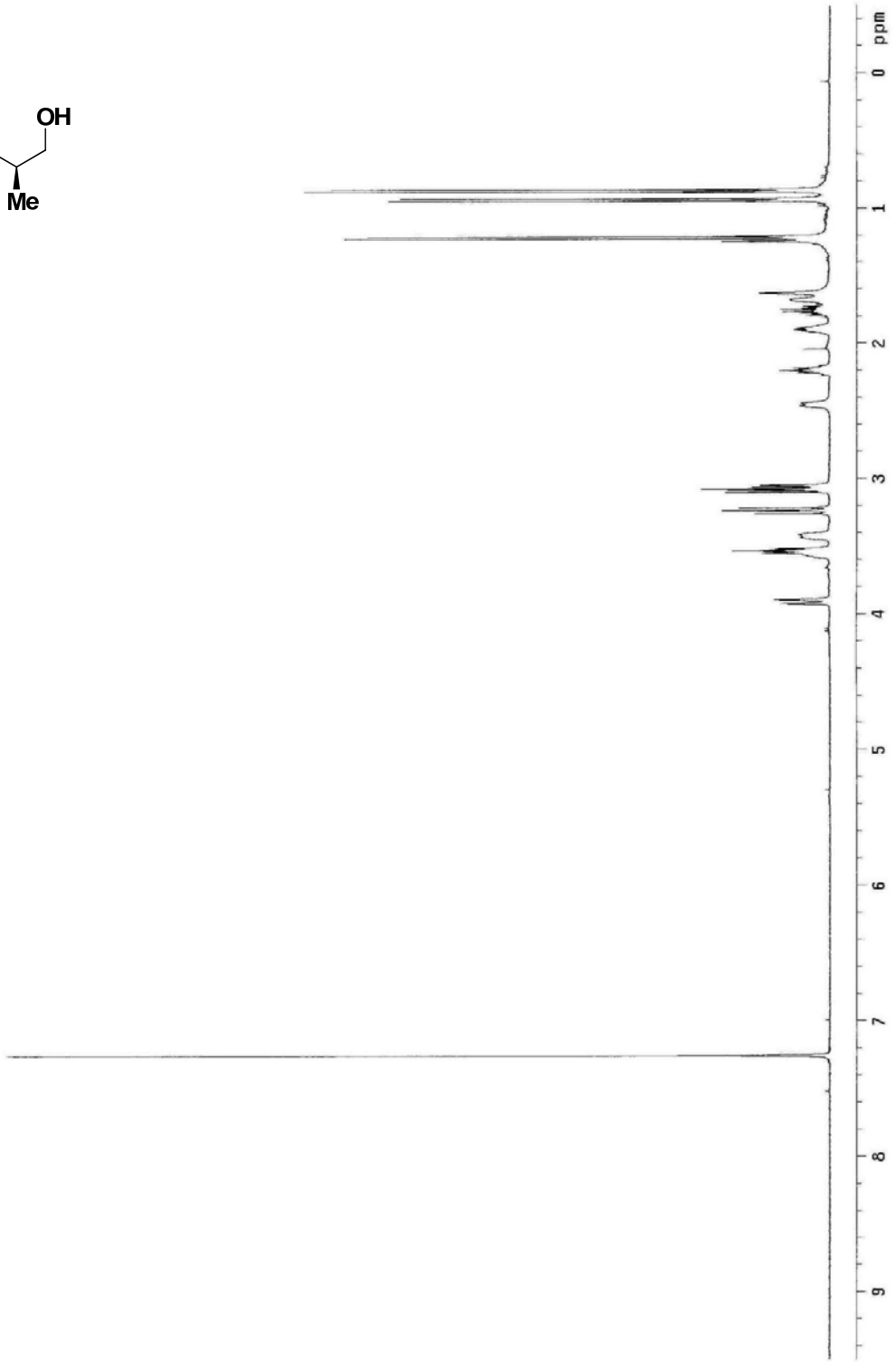

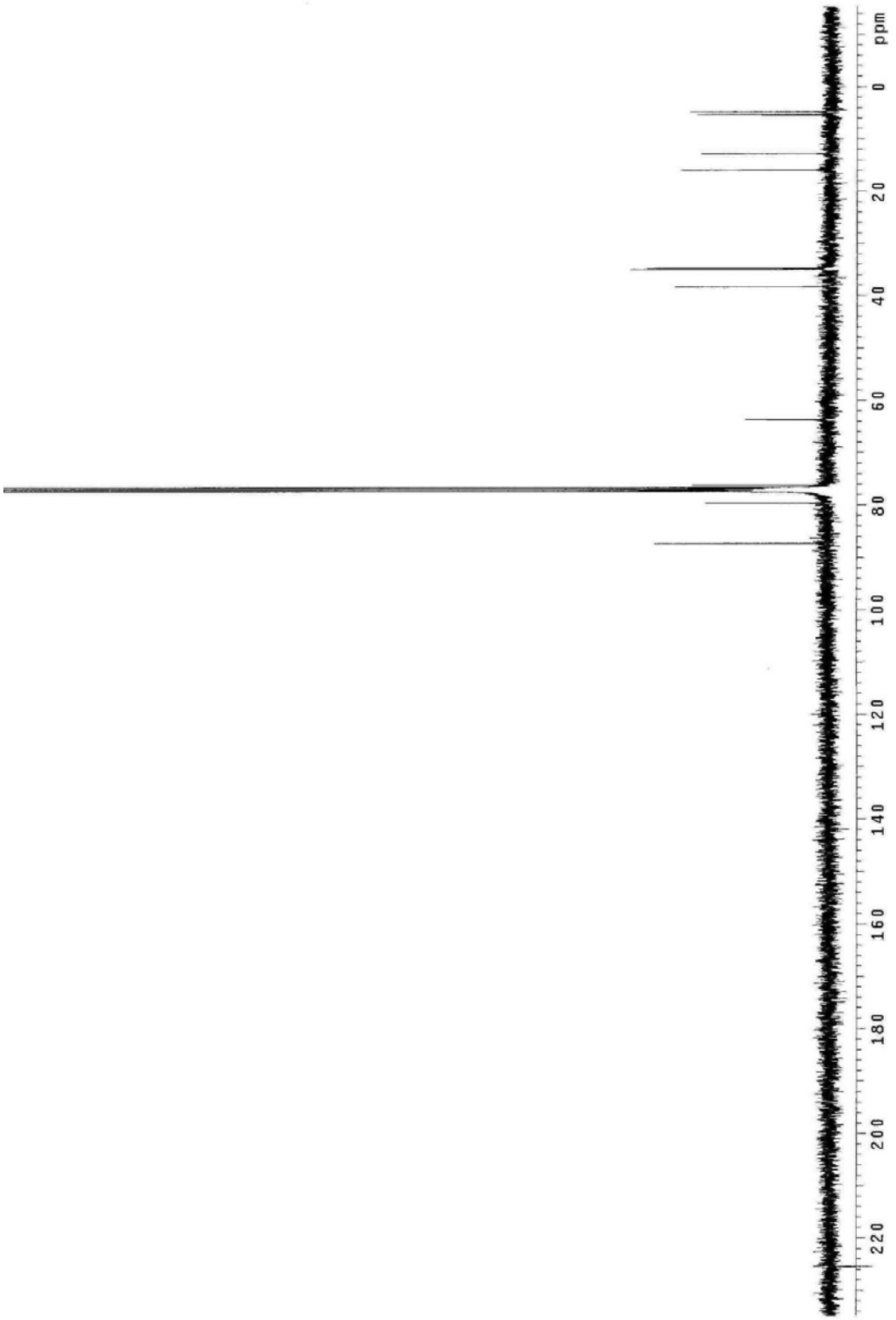
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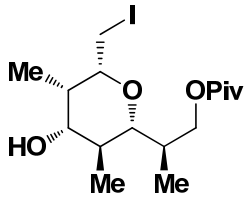
(*R*)-2-((*2R,3S,4S,5S,6R*)-4-Hydroxy-6-(iodomethyl)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)propyl pivalate 4.2.12



A solution of (*2R,3S,4S,5S,6R*)-2-((*R*)-1-hydroxypropan-2-yl)-6-(iodomethyl)-3,5-dimethyltetrahydro-2*H*-pyran-4-ol (100 mg, 0.30 mmol, 100 mol%) in DCM (0.6 mL, 0.5 M) was added pyridine (47.5 mg, 0.60 mmol, 200 mol%) and pivaloyl chloride (43.4 mg, 0.36 mmol, 120 mol%). The reaction mixture was stirred overnight under ambient temperature. Saturated NH_4Cl (5 mL) was added, and the reaction mixture wastransferred to a separatory funnel. The aqueous layer was extracted with DCM (3 ×5 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:10) gave the title compound (108.8 mg, 0.26 mmol) as a colorless oil in 88% yield.

TLC (SiO_2): R_f = 0.7 (ethyl acetate:hexanes, 1:10).

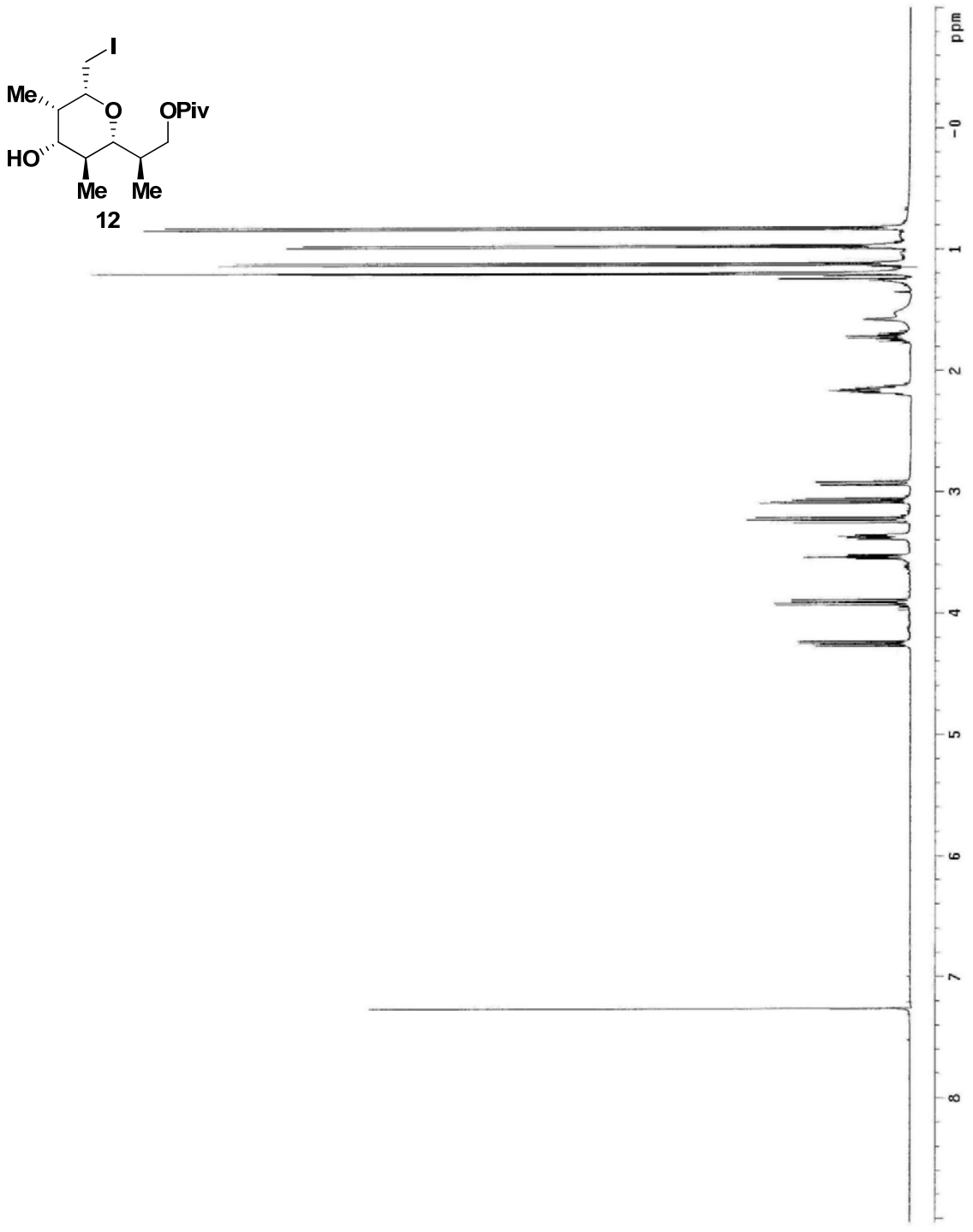
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.25 (dd, *J* = 10.8, 5.6 Hz, 1H), 3.91 (dd, *J* = 10.8, 8.0 Hz, 1H), 3.56-3.52 (m, 1H), 3.39-3.35 (m, 1H), 3.23 (dd, *J* = 10.0, 8.0 Hz, 1H),3.07 (dd, *J* = 10.0, 5.6 Hz, 1H),2.93 (dd, *J* = 10.0, 2.0 Hz, 1H), 2.20-2.11 (m, 2H), 1.76-1.67 (m, 1H), 1.20 (s, 9H), 1.12 (d, *J* = 7.2 Hz, 3H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 178.6, 84.7, 79.1, 76.6, 65.1, 38.7, 38.2, 34.4, 33.4, 27.2, 16.3, 12.7, 5.9, 4.6.

$[\alpha]_D^{26}$ = +27.1 (c = 1.20, $CHCl_3$).

FTIR (neat): υ 3052, 2965, 2927, 1734, 1485, 1400, 1134, 1111, 1080, 1056, 998, 985, 967, 934, 899, 740.

HRMS: (CI) Calcd. for $C_{16}H_{29}O_4I$ $[M]^+$: 412.1111, Found: 412.1115.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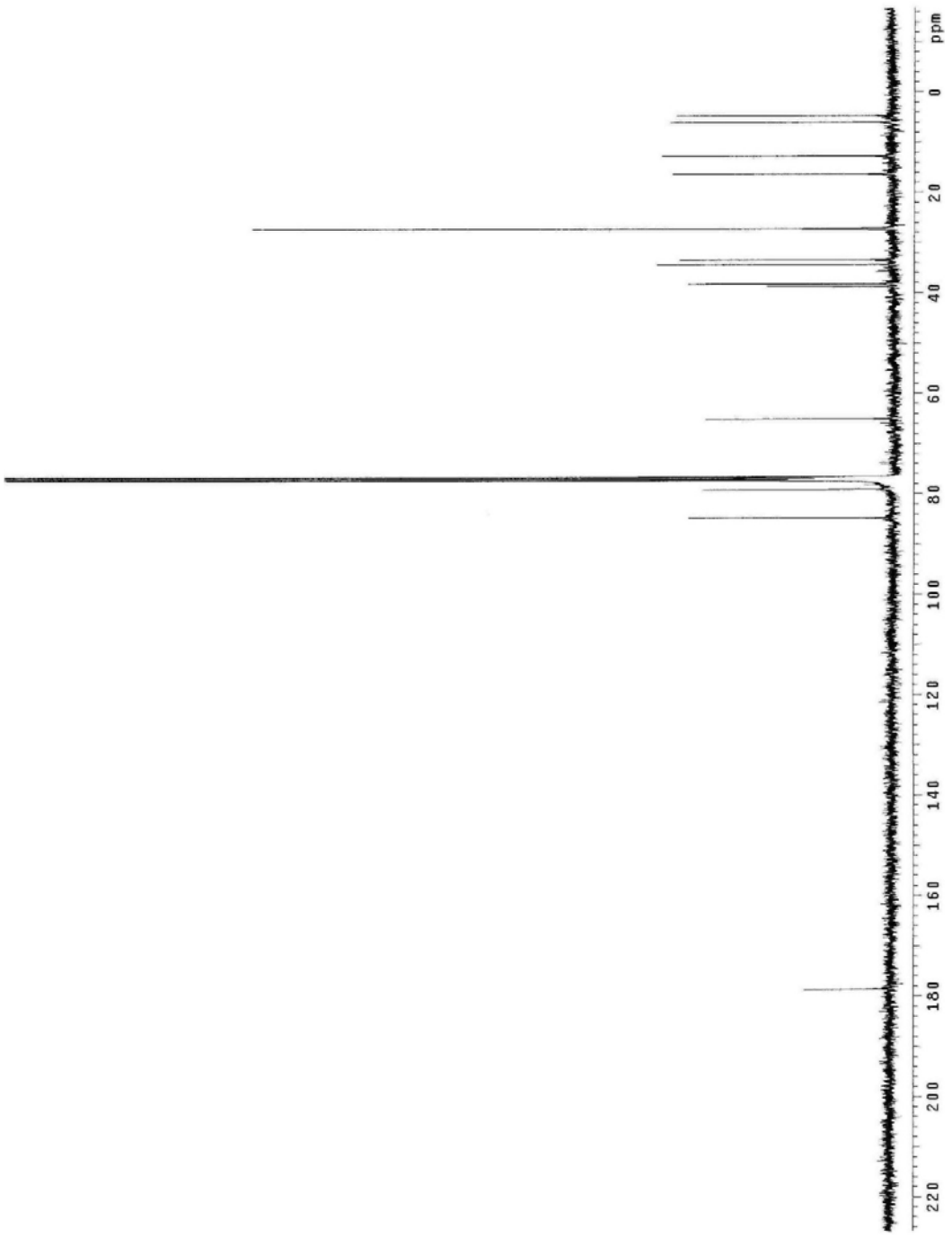
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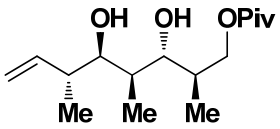
(*2R,3R,4S,5R,6R*)-3,5-Dihydroxy-2,4,6-trimethyloct-7-enyl pivalate 4.2.13



A solution of (*R*)-2-((*2R,3S,4S,5S,6R*)-4-hydroxy-6-(iodomethyl)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)propyl pivalate (85.9 mg, 0.30 mmol, 100 mol%) in EtOH (3 mL, 0.1 M) was added activated Zn (294.3 mg, 4.50 mmol, 1500 mol%) and NH_4Cl (160.5 mg, 3.00 mmol, 1000 mol%). The reaction mixture was heated under refluxing and was allowed to stir overnight. The crude reaction mixture was diluted with ethyl acetate (15 mL) and filtered through a silica plug. The filtrate was concentrated under reduced pressure. Purification by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:5) gave the title compound (68.7 mg, 0.24 mmol) as a colorless oil in 80% yield.

TLC (SiO_2): R_f = 0.3 (ethyl acetate:hexanes, 1:3).

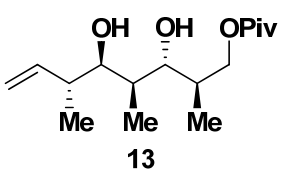
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.69 (dt, *J* = 18.0, 9.2 Hz, 1H), 5.19-5.14 (m, 2H), 4.29-4.20 (m, 2H), 3.61 (d, *J* = 9.2 Hz, 1H), 3.38-3.35 (m, 2H), 2.52 (br, 1H), 2.33-2.23 (m, 1H), 2.07-2.01 (m, 1H),1.95-1.89 (m, 1H), 1.79-1.72 (m, 1H), 1.21 (s, 9H), 1.07 (d, *J* = 7.2 Hz, 3H), 0.95 (d, *J* = 6.4 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 178.9, 141.4, 116.9, 78.0, 73.6, 67.0, 42.5, 38.9, 36.8, 33.5, 27.2, 16.2, 14.1, 10.7.

$[\alpha]_D^{25}$ = -0.4 (c = 1.00, $CHCl_3$).

FTIR (neat): υ 3652, 3314, 2965, 2927, 1750, 1479, 1414, 1389, 1266, 1180, 1091, 1079, 1042, 1000, 993, 812, 735, 679.

HRMS: (CI) Calcd. for $C_{16}H_{29}O_4I$ $[M-H]^+$: 285.2066, Found: 285.2066.



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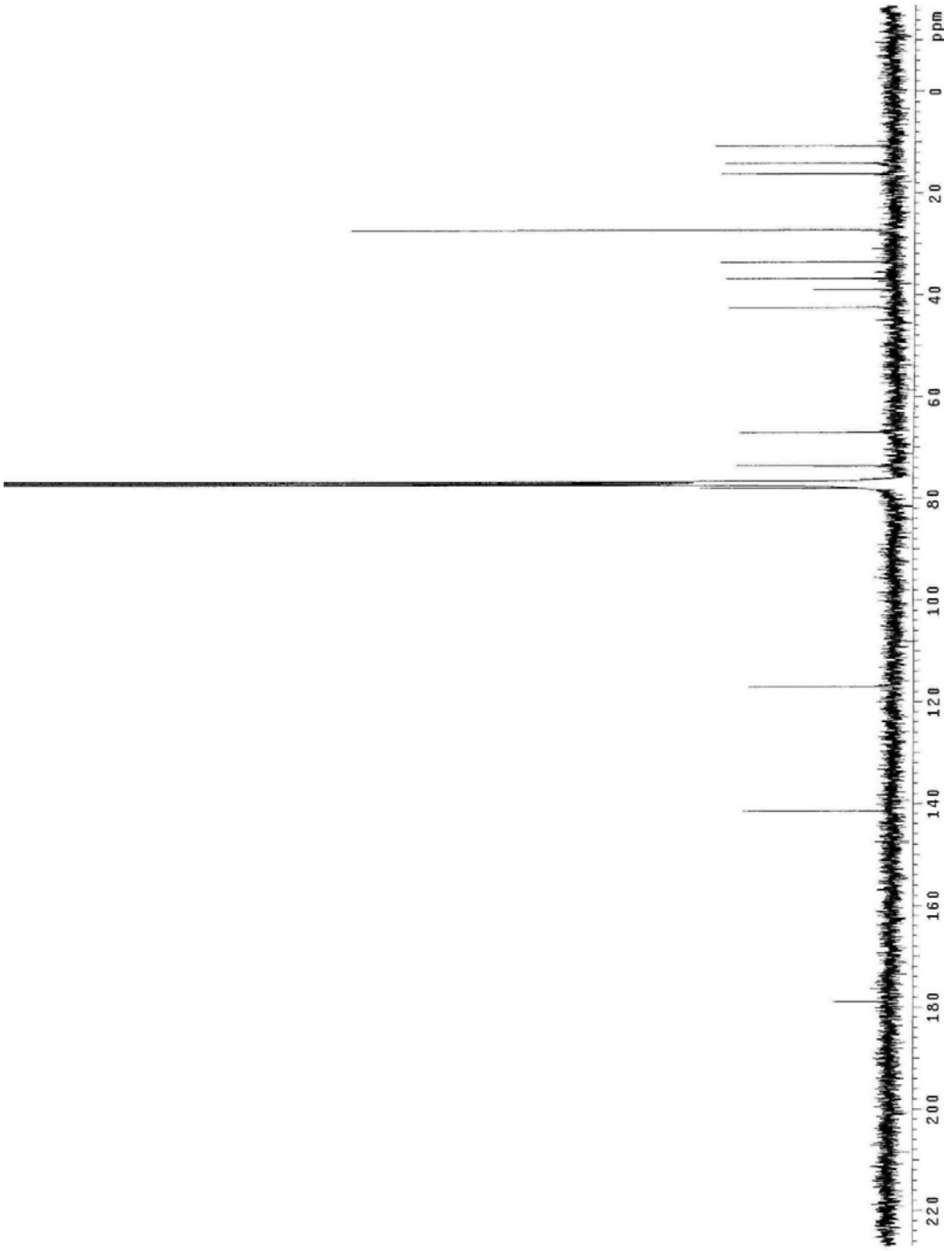
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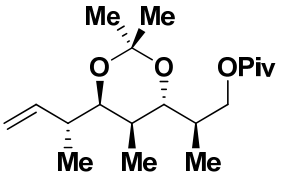
(*R*)-2-((*4R,5S,6R*)-6-((*R*)-But-3-en-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propyl pivalate 4.2.14



A solution of (*2R,3R,4S,5R,6R*)-3,5-dihydroxy-2,4,6-trimethyloct-7-enyl pivalate (28.6 mg, 0.10 mmol, 100 mol%) in DCM (2.0 mL, 0.05 M) was added 2,2-dimethoxypropane (104.2 mg, 1.0 mmol, 1000 mol%) and PPTS (5.0 mg, 0.02 mmol, 20 mol%). The reaction mixture was stirred overnight under ambient temperature. Saturated $NaHCO_3$ (5 mL) was added, and the reaction mixture was transferred to a separatory funnel. The aqueous layer was extracted with DCM (3 ×5 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:20) gave the title compound (31.7 mg, 0.10 mmol) as a colorless oil in 97% yield.

TLC (SiO_2): R_f = 0.6 (ethyl acetate:hexanes, 1:20).

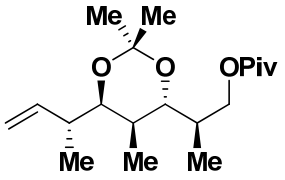
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (ddd, *J* = 17.2, 10.4, 7.2 Hz, 1H), 5.04 (dt, *J* = 17.2, 1.6 Hz, 1H), 4.98 (dt, *J* = 10.4, 1.6 Hz, 1H), 4.15 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.99 (dd, *J* = 10.8, 7.2 Hz, 1H), 3.43 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.21 (t, *J* = 7.6 Hz, 1H), 2.30-2.21 (m, 1H), 1.99-1.85 (m, 2H), 1.29 (s, 3H), 1.25 (s, 3H), 1.20 (s, 9H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 178.6, 142.1, 113.5, 100.6, 76.2, 73.1, 66.0, 38.8, 37.3, 36.9, 35.6, 27.2, 25.1, 23.3, 15.7, 13.8, 12.5.

$[\alpha]_D^{25}$ = -7.2 (c = 0.71, $CHCl_3$).

FTIR (neat): υ 3030, 2965, 2927, 1744, 1458, 1415, 1389, 1266, 1180, 1131, 1097, 1059, 1038, 1009, 983, 967, 937, 890, 803, 736, 697.

HRMS: (CI) Calcd. for $C_{19}H_{34}O_4I$ $[M]^+$: 326.2458, Found: 326.2459.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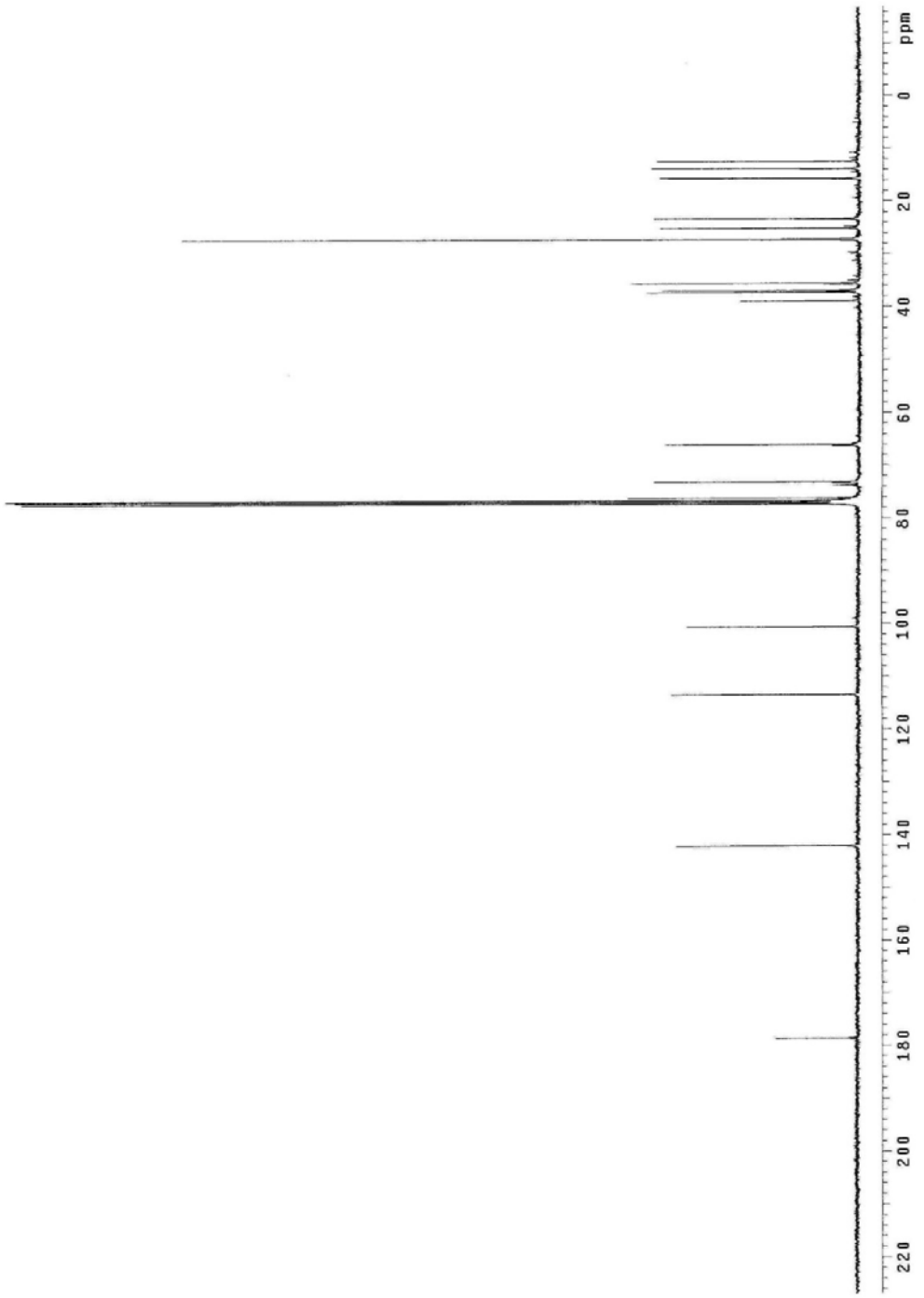
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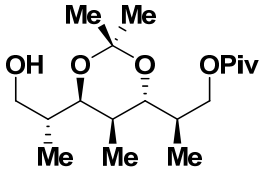
(*R*)-2-((*4R,5S,6R*)-6-((*R*)-1-Hydroxypropan-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propyl pivalate 4.2.15



A solution of (*R*)-2-((*4R,5S,6R*)-6-((*R*)-but-3-en-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propyl pivalate (49.0 mg, 0.15 mmol, 100 mol%) in DCM:MeOH (1:1, 3.0 mL, 0.05 M) was added 3-5 drops of a methanolic solution of Sudan III (1.5 nM), which resulted in a light pink coloration. O_3 (2.0 $L.min^{-1}$, 15 V) was bubbled through the solution until the color changed from pink to colorless. The reaction mixture was purged with argon, and $NaBH_4$ (56.8 mg, 1.5 mmol, 1000 mol%) was added. The reaction warmed to ambient temperature and was allowed to stir overnight. Brine (5 mL) was added and the reaction mixture was transferred to a separatory funnel. The aqueous layer was extracted with DCM (3 × 15 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:1) gave the title compound (44.6 mg, 0.14 mmol) as a colorless oil in 90% yield.

TLC (SiO_2): R_f = 0.5 (ethyl acetate:hexanes, 1:3).

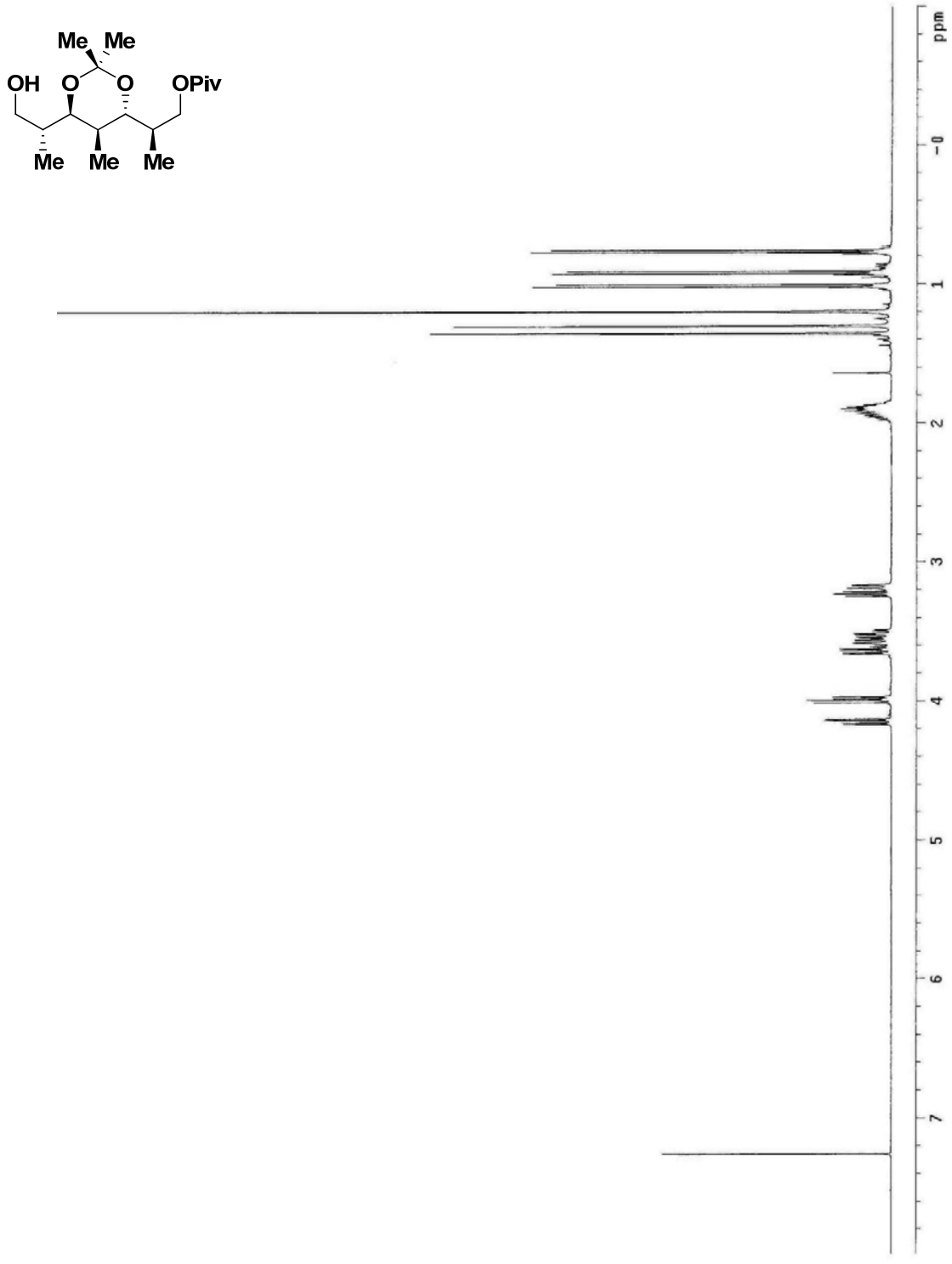
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.15 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.99 (dd, *J* = 10.8, 6.8 Hz, 1H), 3.64 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.61-3.49 (m, 2H), 3.23 (dd, *J* = 6.8, 6.0 Hz, 1H), 3.18 (dd, *J* = 10.0, 2.0 Hz, 1H), 1.98-1.84 (m, 3H), 1.36 (s, 3H), 1.30 (s, 3H), 1.20 (s, 9H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 178.5, 100.7, 76.2, 76.0, 69.1, 65.8, 38.8, 37.2, 35.5, 34.9, 27.2, 25.4, 23.3, 13.7, 12.6, 12.5.

$[\alpha]_D^{25}$ = -6.2 (c = 0.75, $CHCl_3$).

FTIR (neat): υ 3500, 3033, 2927, 2845, 1744, 1312, 1270, 1164, 1025, 1001, 894, 732, 697.

HRMS: (CI) Calcd. for $C_{18}H_{35}O_5I$ $[M+H]^+$: 331.2485, Found: 331.2479.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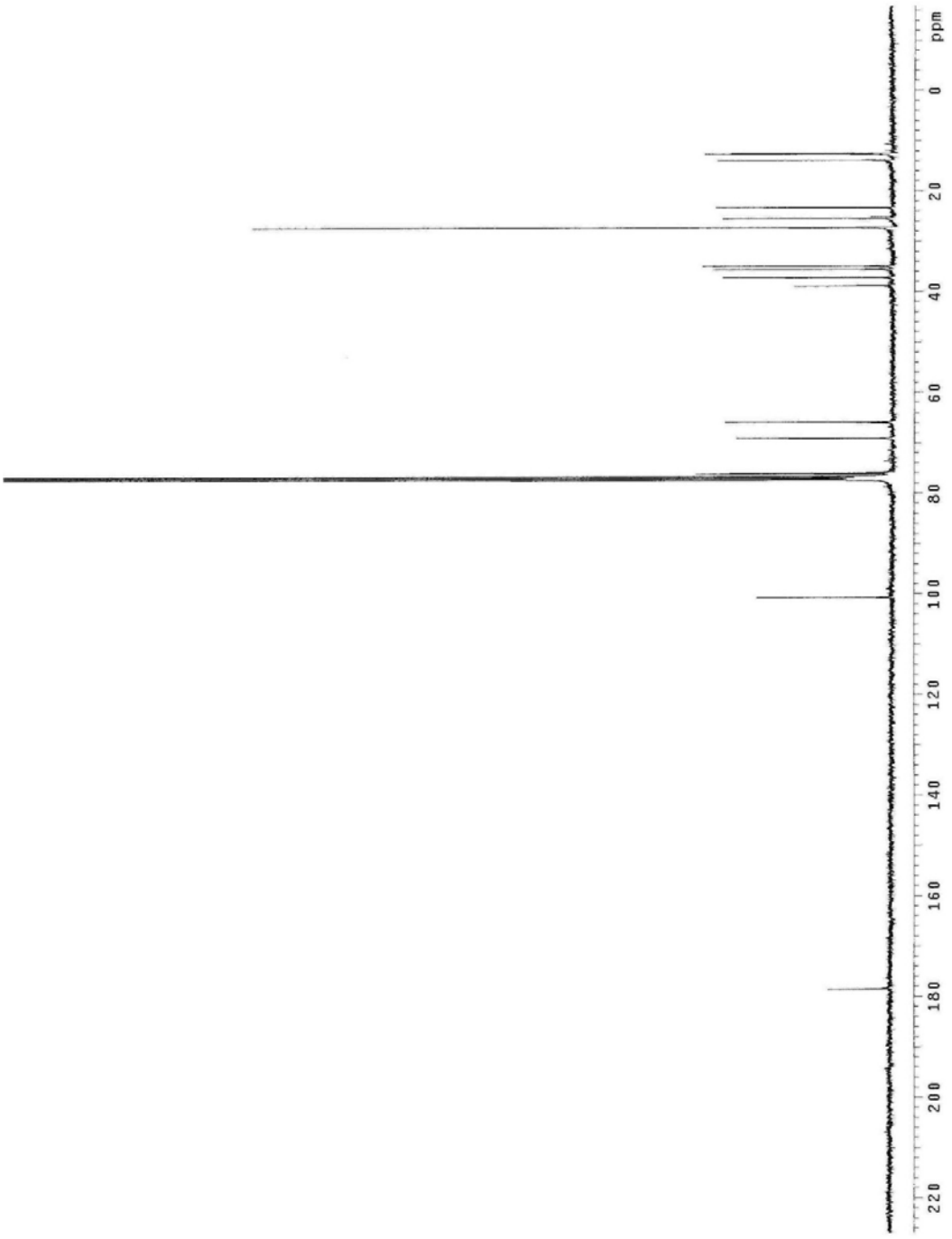
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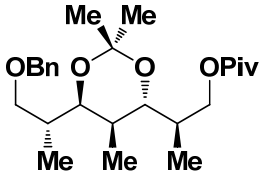
(*R*)-2-((*4R,5S,6R*)-6-((*R*)-1-(benzyloxy)propan-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propyl pivalate (Scytophycin C C19-C25 Fragment) 4.2.16



A solution of (*R*)-2-((*4R,5S,6R*)-6-((*R*)-1-hydroxypropan-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propyl pivalate (14.5 mg, 0.04 mmol, 100 mol%) in DCM (2.0 mL, 0.02 M) was added freshly made benzyl 2,2,2-trichloroacetimidate (30.3 mg, 0.12 mmol, 300 mol%) and camphorsulfonic acid (1.0 mg, 0.004 mmol, 10 mol%). The reaction mixture was stirred overnight under ambient temperature. Saturated $NaHCO_3$ (5 mL) was added, and the reaction mixture was transferred to a separatory funnel. The aqueous layer was extracted with diethyl ether (3 ×5 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:15) gave the title compound (13.1 mg, 0.03 mmol) as a colorless oil in 78% yield.

TLC (SiO_2): R_f = 0.5 (ethyl acetate:hexanes, 1:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24-7.25 (m, 5H), 4.48 (s, 2H), 4.16 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.99 (dd, *J* = 10.8, 6.8 Hz, 1H),3.62 (dd, *J* = 10.8, 4.4 Hz, 1H),3.57 (dd, *J* = 8.8, 2.8 Hz, 1H), 3.20 (t, *J* = 6.4 Hz, 1H), 1.94 (qddd, *J* = 6.8, 6.8, 6.8, 4.4 Hz, 1H), 1.86 (qdd, *J* = 6.8, 6.8, 4.4 Hz, 1H), 1.84 (dqdd, *J* = 10.8, 6.8, 6.8, 2.2 Hz, 1H), 1.29 (s, 3H), 1.25 (s, 3H), 1.20 (s, 9H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H).

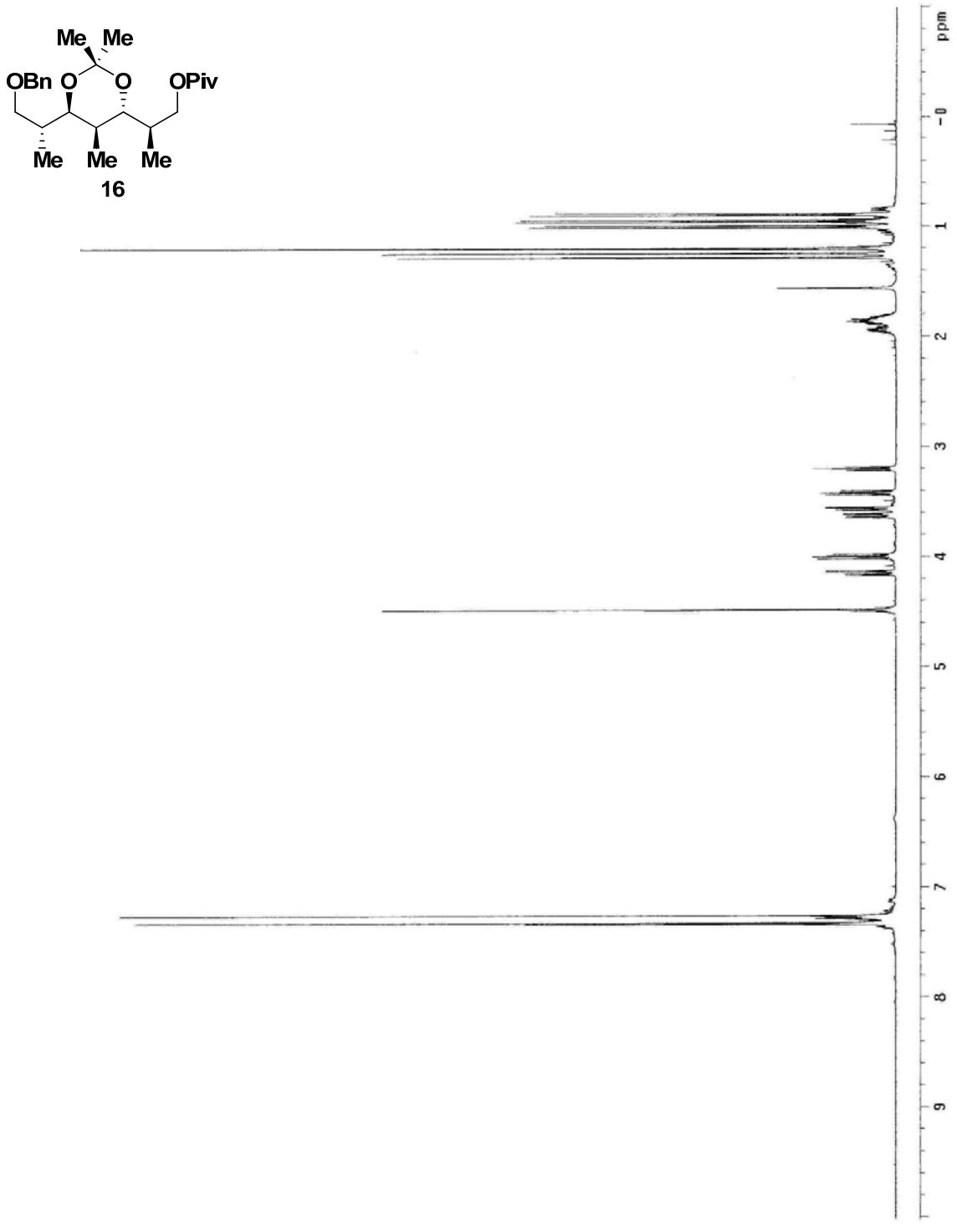
^{13}C NMR(100 MHz, $CDCl_3$): δ 178.6, 138.9, 128.2, 127.5, 127.3, 100.5, 76.4, 73.2, 72.5, 70.0, 66.0, 38.8, 37.3, 35.3, 33.7, 27.2, 25.1, 23.3, 13.8, 13.4, 12.4.

$[\alpha]_D^{26}$ = -2.0 (c = 1.1, $CHCl_3$).

FTIR (neat): υ 3034, 2973, 2855, 1737, 1160, 1026, 999, 748, 699.

HRMS: (CI) Calcd. for $C_{25}H_{41}O_3I$ $[M+H]^+$: 421.2955, Found: 421.2955.

The spectroscopic properties of this compound were consistent with the data available in the literature.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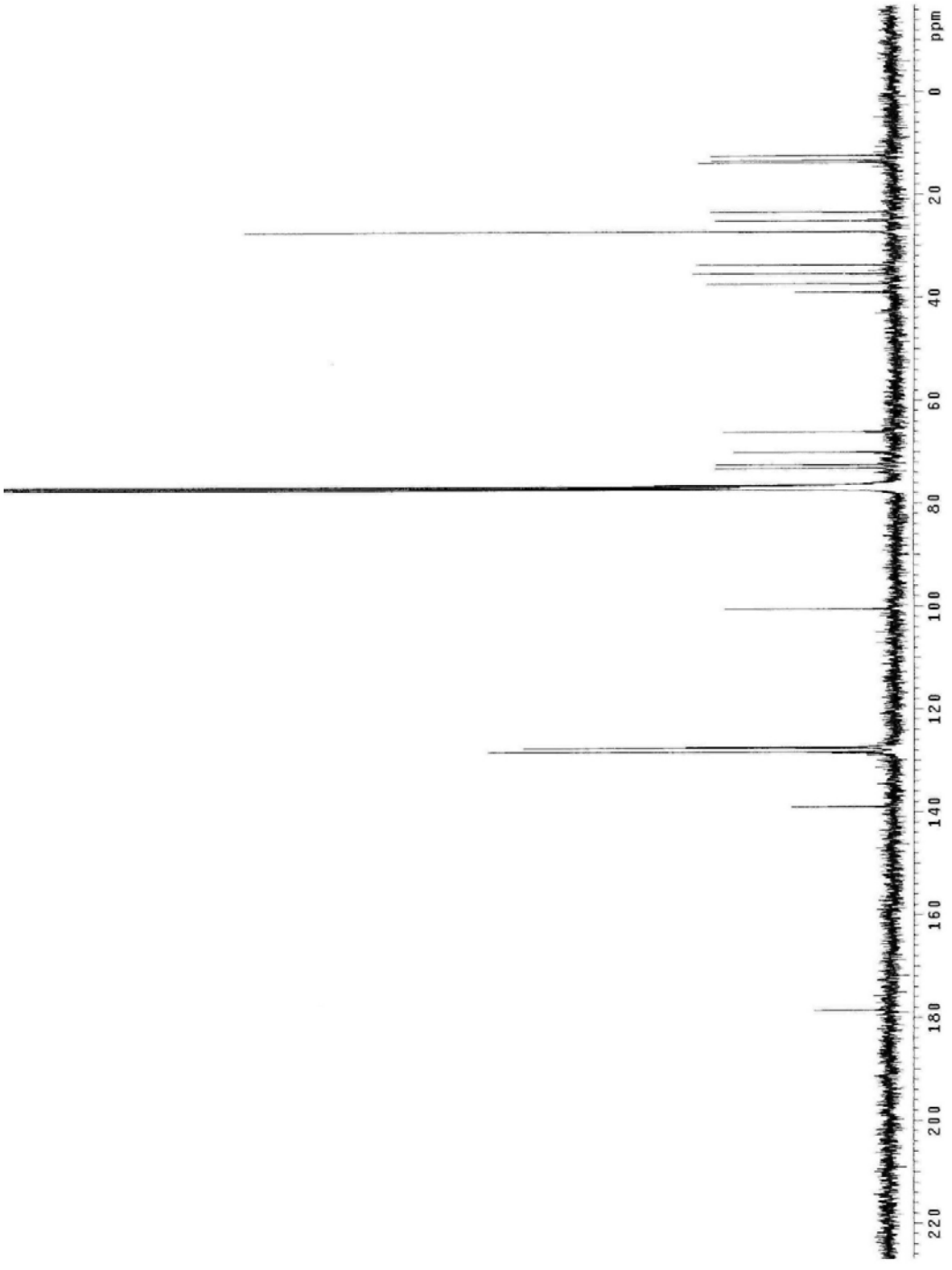
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CHAPTER 5: TOTAL SYNTHESIS OF 6-DEOXYERYTHRONOLIDE B VIA C-C BOND-FORMING TRANSFER HYDROGENATION[1]

5.1 INTRODUCTION

In 1952, the pharmaceutical company Eli Lily commercialized the first macrolide antibiotic, erythromycin A.[2] Beyond its impact on human medicine, the challenges in chemical synthesis posed by erythromycin A and related polyketides propelled advances in acyclic stereocontrol *via* carbonyl addition, especially aldol bond constructions and crotylation methods.[3] Perhaps fueled further by Woodward's dim assessment of the prospect of accessing erythromycin A through chemical synthesis,[4] the erythromycins have become inextricably tied to the evolution of synthetic organic chemistry and their total syntheses are widely regarded as benchmarks for the state-of-the-art. As illustrated in total syntheses of erythromycin A[5] and B[6], erythronolide A[7] and B[8], (*9S*)-dihydroerythronolide A[9] and their biogenic precursor 6-deoxyerythronolide B[10], tremendous strides have been made over the past 30 years. However, all reported syntheses remain well over 20 steps in length, suggesting the influence of the erythromycins on chemical synthesis will persist into the future (Figure 1.1.3).

In the course of exploring C-C bond forming hydrogenations and transfer hydrogenations beyond hydroformylation,[11] our laboratory developed a suite of methods for stereoselective polyketide construction, including methods for carbonyl crotylation *via* redox triggered C-C coupling of primary alcohols and α-methyl allyl acetate **5.5** or

butadiene using iridium[12] and ruthenium[13] catalysts, respectively. These studies evoked an exceptionally powerful transformation that has no counterpart in conventional allylmetal chemistry:[3] the *anti*-diastereo- and enantioselective iridium catalyzed *double crotylation* of 2-methyl-1,3-propanediol **5.6** to form polypropionate stereoquintets.[12c] To benchmark the utility of this method *vis-à-vis* polyketide construction, it was applied to the preparation of 6-deoxyerythronolide B. This undertaking has resulted in the most concise route to any erythronolide reported, to date.[2,5-10]

Before we started investigated our effort into current synthetic route, several failed attempts had also been carried out by our lab. The methyl group on C10 significantly decreased the reactivity of this type of substrate; hence introducing the methyl at fairly late stage would be more promising strategy (Figure 5.1).

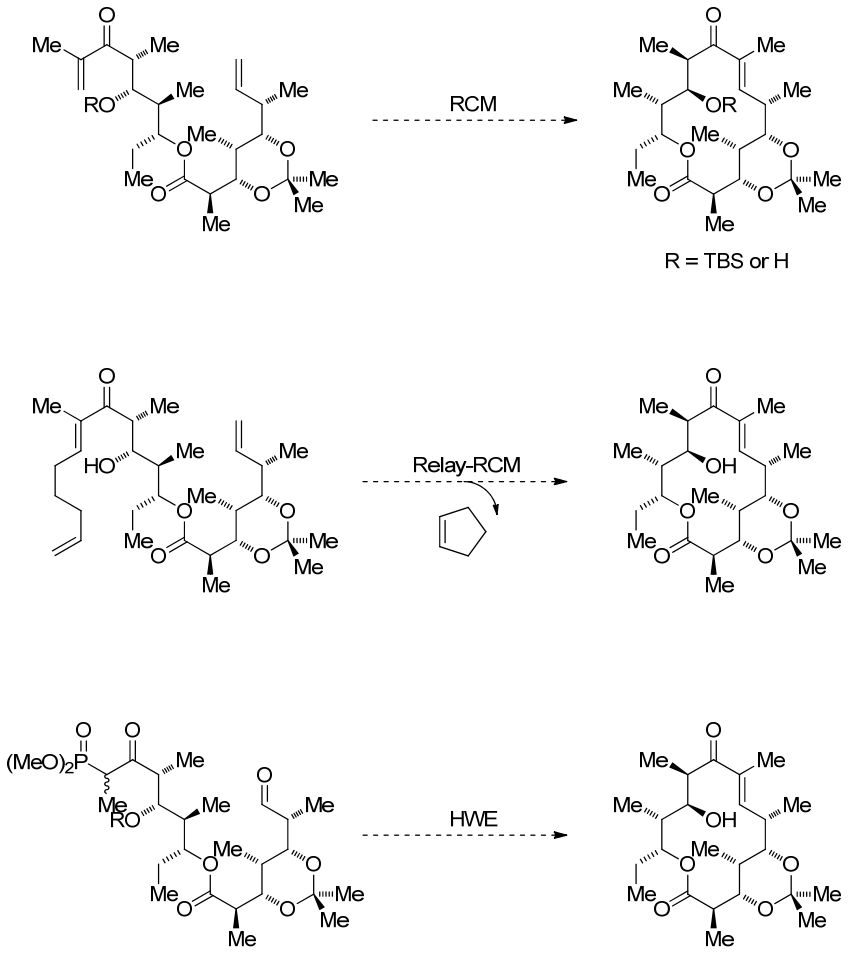
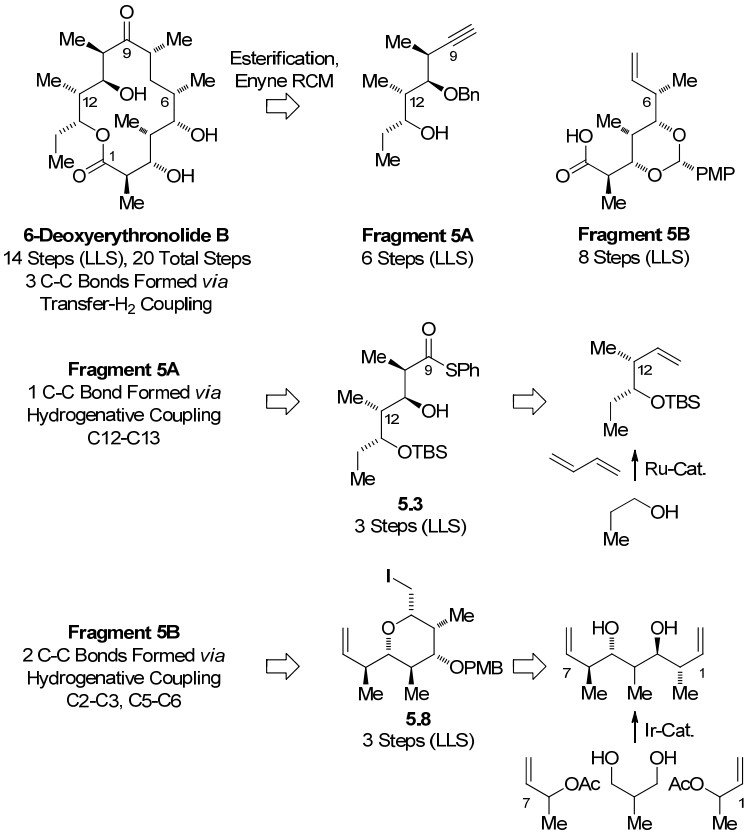


Figure 5.1 Failed attempts to construct 14-membered lactone.

5.2 RETROSYNTHETIC ANALYSIS

Retrosynthetically, a convergent assembly of 6-deoxyerythronolide B from Fragments **5A** and **5B** was envisioned through esterification followed by ring-closing

enyne metathesis to form the 14-membered macrolide.[14] Fragment **5A** is prepared in 6 steps from *n*-propanol **5.1** through successive introduction of propionate subunits *via* ruthenium catalyzed butadiene mediated *syn*-crotylation[13d] followed by substrate directed *syn*-aldol addition[15] to form thiol ester **5.3**, which incorporates the 4 contiguous stereogenic centers spanning C10-C13. Fragment **5B**, which incorporates the 5-contiguous stereogenic centers spanning C2-C6, is prepared in 8 steps from 2-methyl-1,3-propane diol **5.6** *via* iridium catalyzed double crotylation followed by iodoetherification and alkene oxidative cleavage to form the carboxylic acid (Scheme 5.1).[12c]

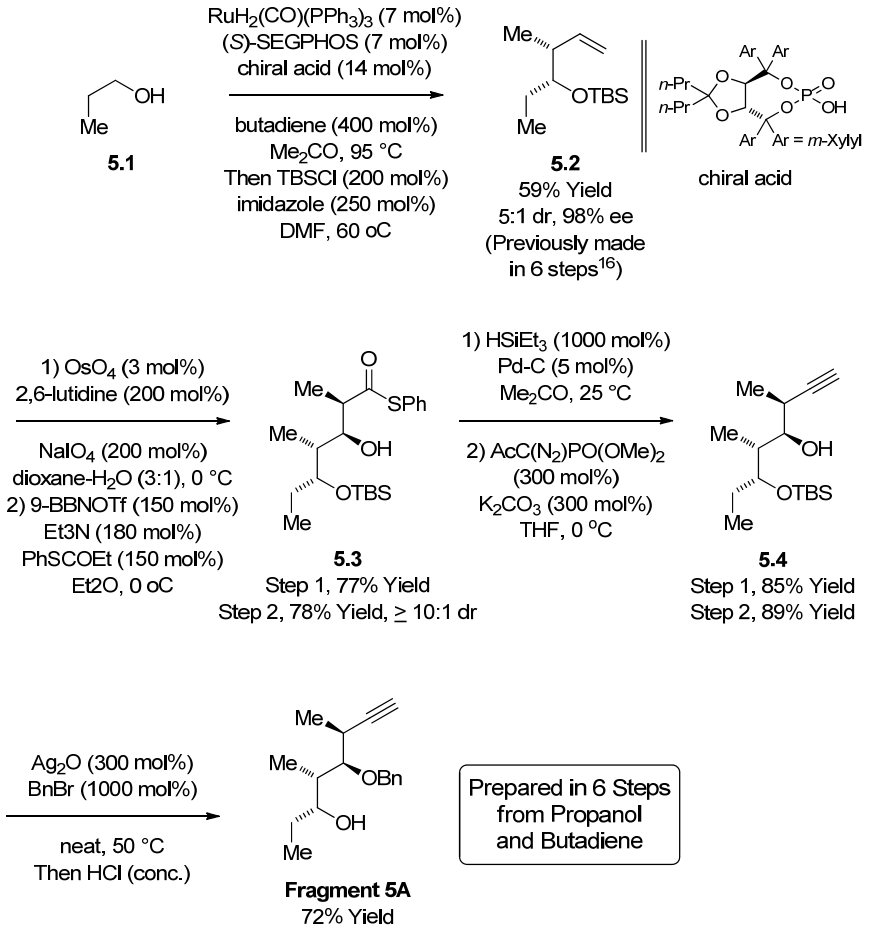


Scheme 5.1 Retrosynthetic analysis of deoxyerythronolide B highlighting C-C bonds formed *via* hydrogenative coupling.

5.3 FRAGMENTS SYNTHESIS

5.3.1 ALCOHOL FRAGMENT 5A SYNTHESIS

The synthesis of Fragment **5A** begins with the butadiene mediated hydrohydroxyalkylation of *n*-propanol **5.1** to form the product of *syn*-crotylation (Scheme 5.2).[13d] As the resulting secondary alcohol is quite volatile, reagents promoting formation of the TBS ether **5.2** were added to the reaction mixture after the C-C coupling was complete, enabling direct acquisition of TBS ether **5.2** from *n*-propanol in 59% isolated yield with 5:1 *syn*-diastereoselectivity and 98% enantiomeric excess.[13d,16] Oxidative cleavage of the terminal olefin followed by treatment of the resulting aldehyde with the (*E*)-boron enolate derived from *S*-phenyl propanethioate delivered the product of *syn*-aldol addition **5.3** with only trace quantities of the *anti*-diastereomer detected by ^{1}H NMR analysis.[15] The thiol ester **5.3** was converted to the β-hydroxy aldehyde,[17] which was exposed to the Ohira-Bestmann reagent to form the homopropargyl alcohol **5.4** without protection of the hydroxyl moiety.[18] Finally, benzylation of homopropargyl alcohol **5.4** accompanied by acidic hydrolysis of the TBS ether in the course of isolation provides Fragment **5A**. An even more concise route to Fragment **5A** potentially involves 1,3-enyne hydrohydroxyalkylation to form the C10-C11 bond with concomitant installation of the alkyne, however, this chemistry has not yet been adapted to the use of chiral β-stereogenic alcohols (Scheme 5.2).[19]

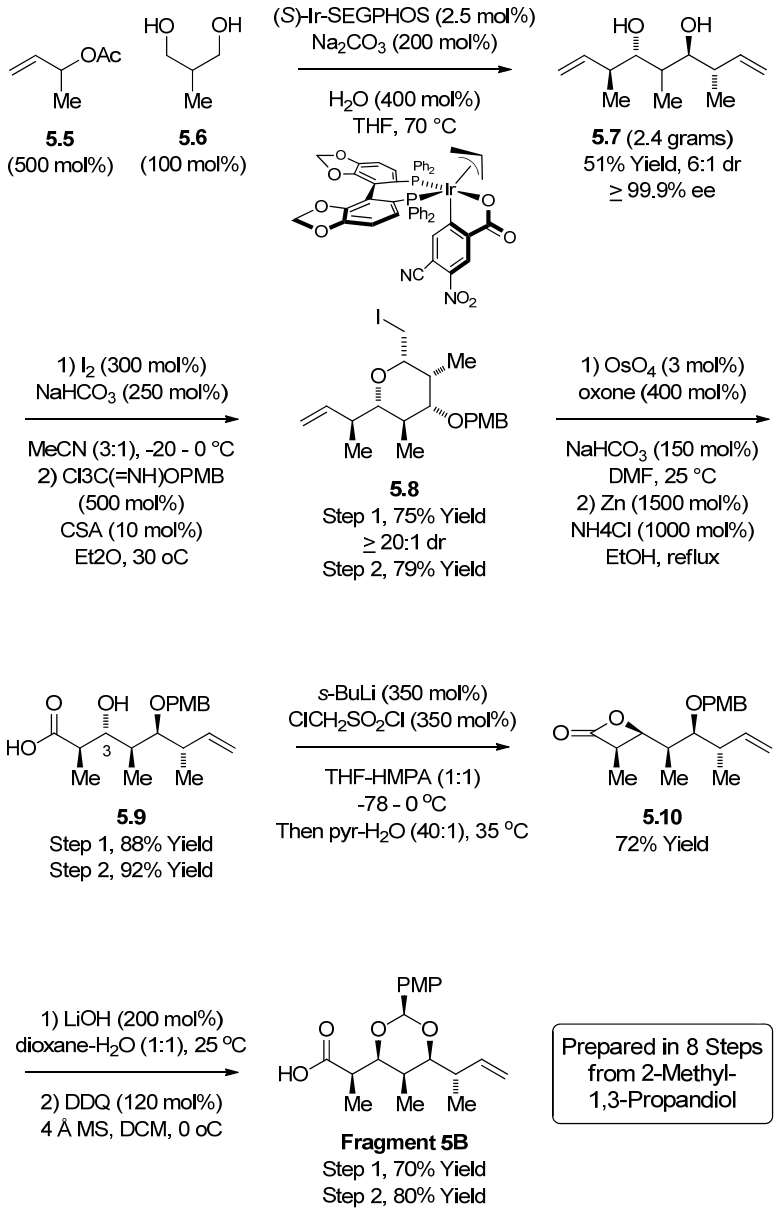


Scheme 5.2 Alcohol fragment **5A** synthesis.

5.3.2 ACID FRAGMENT 5B SYNTHESIS

The synthesis of Fragment **5B** begins with the *anti*-diastereo- and enantioselective iridium catalyzed double crotylation of 2-methyl-1,3-propanediol **6** to furnish the *pseudo*-C_2-symmetric diol **5.7** (Scheme 5.3).[12c] The diol **5.7** is produced as a single enantiomer as determined by GC, as the minor enantiomer of the mono-adduct is converted to the *pseudo-meso*-diastereomer.[20] Iodoetherification of **5.7**, which differentiates the alkene termini and diol moieties and defines the nonstereogenic chirotopic center at C4,

followed by benzylation delivers pyran **5.8**. Osmium catalyzed oxidative cleavage of the olefin to form the carboxylic acid[21] followed by zinc mediated reductive cleavage of the iodoether provides the β-hydroxy required. To this end, conversion of **5.9** to the β-lactone **5.10** was attempted under Mitsunobu conditions, however, decarboxylative Grob type elimination to the *cis*-alkene was formed in over 70% yield.[22] Treatment of the dianion of **5.9** with methanesulfonyl chloride[23] delivered the β-lactone **5.10** in 15-20% yield along with recovered β-hydroxy acid **5.9**, suggesting a more electrophilic sulfonylchloride was required. Indeed, use of chloromethanesulfonyl chloride led to the formation of β-lactone **5.10** in 72% yield. It was our hope to directly exploit β-lactone **5.10** in the acylation of Fragment **5A**. However, although related β-lactone ring openings are known,[24] as we learned, *cis*-disubstituted β-lactones are recalcitrant acylating agents,[24b] and so β-lactone **5.10** was converted to the carboxylic acid Fragment **5B** (Scheme 5.3).

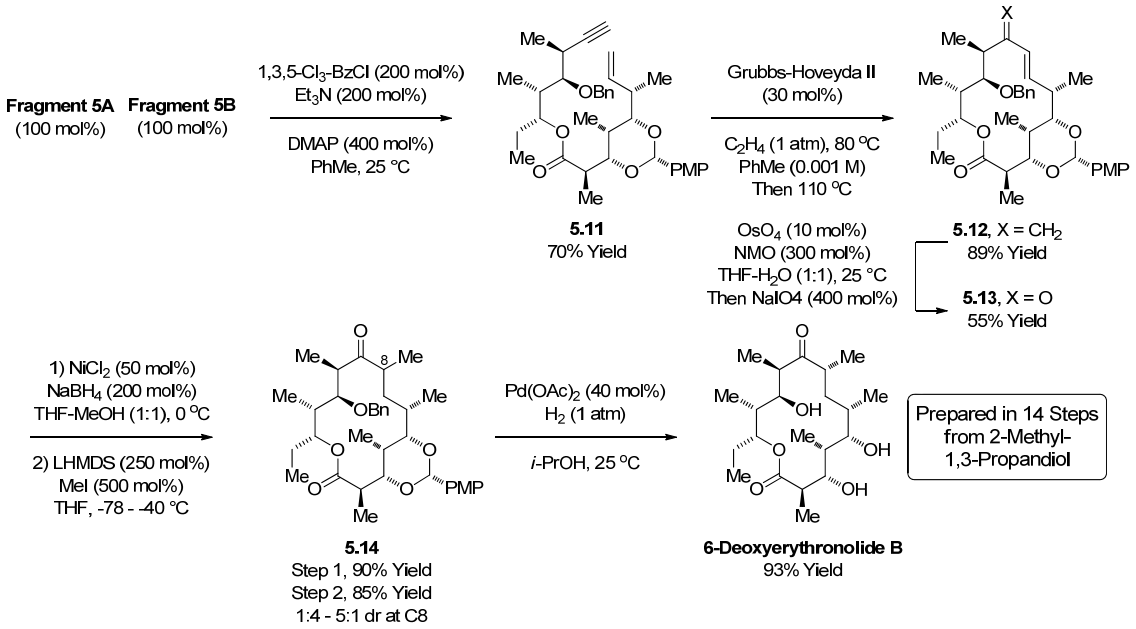


Scheme 5.3 Acid fragment **5B** synthesis.

5.4 FRAGMENTS UNION & END GAME

The convergent assembly of Fragments **5A** and **5B** is achieved through esterification under Yamaguchi's conditions to form the tethered enyne **5.11** (Scheme 5.4).[25] Initial attempts at ring-closing enyne metathesis[14] in the absence of ethylene led to isomerization of the terminal olefin. Under an atmosphere of ethylene at 80 ^{o}C the terminal alkyne is converted to the conjugated diene in nearly quantitative yield, but macrocyclization is not observed. Hence, upon complete conversion to the conjugated diene at 80 ^{o}C, the reaction vessel was purged with nitrogen and the reaction temperature was increased to 110 ^{o}C, which induced formation of the 14-membered macrolide **5.12** as a single regioisomer in a remarkable 89% yield. Osmium catalyzed oxidative cleavage of the C9 methylidene residue provides the conjugated enone **5.13**.[21] Reductive methylation of enone **5.13** to form ketone **5.14** under the conditions of dissolving metal reduction or through the agency of arene anion radicals was explored.[26] Although efficient reductive alkylation was achieved in a model system (4,4-dimethylcyclohexenone), enone **5.13** underwent benzyl cleavage or decomposed upon exposure to dissolving metal conditions, and upon treatment with arene anion radicals enone **5.13** was converted to the product of enone 1,2-reduction. Consequently, the conversion of enone **5.13** to ketone **5.14** was accomplished by P2-nickel catalyzed hydrogenation[27] followed by conventional enolate methylation. Interestingly, highly variable levels of diastereoselectivity were associated with the newly formed C8-stereocenter of ketone **5.14**, suggesting facile epimerization at this position. Indeed, irrespective of the diastereomeric ratio at C8, exposure of ketone **5.14** to the slightly acidic conditions of palladium catalyzed homogenous hydrogen provides 6- deoxyerythronlide B in 93% isolated yield as a single diastereomer. Thus, 6-

deoxyerythronlide B is prepared in 14 steps (longest linear sequence) and 20 total steps, representing the most concise route to any erythromycin family member reported, to date.



Scheme 5.4 Fragments union and end game.

5.5 SUMMARY

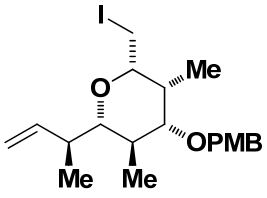
New reactivity is the principal basis for new functional group interconversions and, hence, new strategies that can shift the retrosynthetic paradigm, ultimately simplifying longstanding challenges in chemical synthesis. Successfully utilizing double crotylation strategy and *syn*-crotylation mediated by 1,3-butadiene, our lab has established the most concise assembly of 6-deoxyerythronolide B. This work also represents the shorteset route towards erythronolide family natural products, to date.

5 .6 EXPERIMENTAL SECTION

General Methods

All reactions were run under an atmosphere of Argon. Tetrahydrofuran (THF) and toluene were obtained from Pure-Solv MD-5 Solvent Purification System (Innovative Technology). Anhydrous solvents were transferred by an oven-dried syringe. Sealed tubes (13x100 mm) were purchased from Fischer Scientific and were dried in an oven overnight and cooled under a stream of nitrogen prior to use. Commercially available allyl acetate (Aldrich) was purified by distillation prior to use. Cesium carbonate was purchased from Alfa Aesar and was used directly without further purification. Isopropanol (Fisher) was purified by distillation prior to use. Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F_{254}). Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M or M-H) or a suitable fragment ion. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) spectra were recorded with a Varian Gemini (400 MHz) spectrometer for $CDCl_3$ solutions and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δ_H (7.26 ppm) and $CDCl_3$ δ_C (77.0 ppm), respectively, as internal standards. Coupling constants are reported in Hertz (Hz).

(*2S,3R,4R,5R,6S*)-2-((*S*)-but-3-en-2-yl)-6-(iodomethyl)-4-((4-methoxybenzyl)oxy)-3,5-dimethyltetrahydro-2*H*-pyran



5.8

A solution of (*2S,3R,4R,5R,6S*)-2-((*S*)-but-3-en-2-yl)-6-(iodomethyl)-3,5-dimethyltetrahydro-2*H*-pyran-4-ol (628 mg, 2.00 mmol, 100 mol%) and PMB-imidate (2825.5 mg, 10.00 mmol, 500 mol%) in diethyl ether (6.7 mL, 0.30 M) was heated to 30 °C. To this solution was added camphorsulfonic acid (46.5 mg, 0.2 mmol, 10 mol%) in one portion. The reaction was stirred at 30 °C overnight. Saturated aqueous $NaHCO_3$ was added and the reaction mixture was transferred to a separatory funnel. The aqueous phase was extracted with DCM (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:20) to give the title compound (702.1 mg, 1.58 mmol) as a colorless oil in 79% yield.

TLC (SiO_2): R_f = 0.72 (ethyl acetate:hexanes, 1:3).

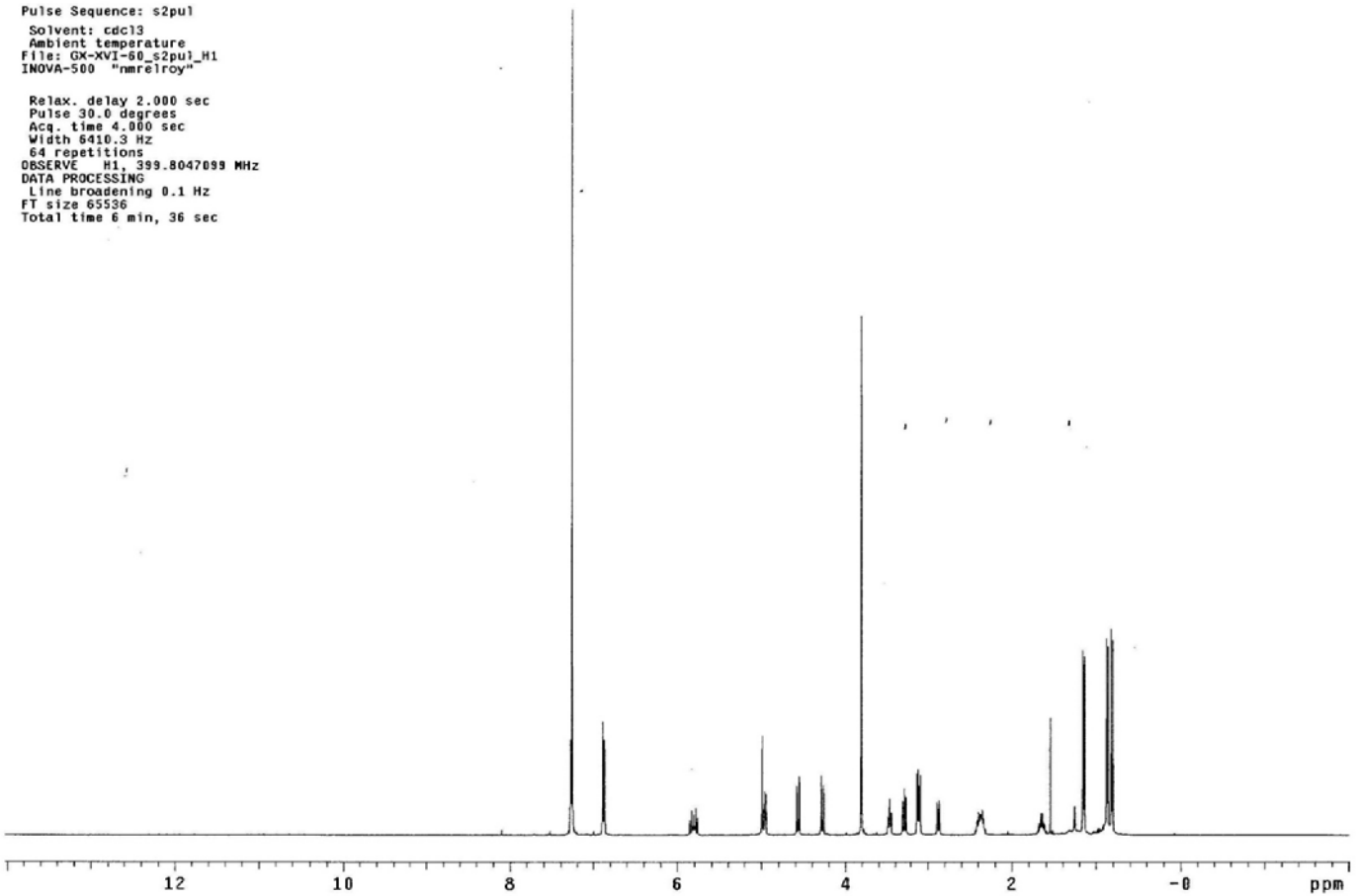
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.28-7.26 (m, 2H), 6.89-6.86 (m, 2H), 5.81 (dt, *J* = 18.0, 9.2 Hz, 1H), 4.99-4.95 (m, 2H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.28 (d, *J* = 11.2 Hz, 1H), 3.81 (s, 3H), 3.47 (ddd, *J* = 8.0, 6.0, 2.0 Hz, 1H), 3.27 (dd, *J* = 10.0, 8.0 Hz, 1H), 3.11 (dd, *J* = 10.0, 6.4 Hz, 1H), 2.87 (dd, *J* = 10.4, 2.0 Hz, 1H), 2.43-2.32 (m, 2H), 1.70-1.60 (m, 1H), 1.15 (d, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 159.2, 139.2, 130.5, 129.4, 115.2, 113.8, 85.4, 82.9, 78.6, 69.7, 55.3, 39.9, 33.8, 32.2, 18.7, 12.6, 6.6, 4.9.

$[\alpha]_D^{25}$ = +51.2 (c = 0.58, $CHCl_3$).

FTIR (neat): υ3100, 2977, 2952, 2332, 1638, 1458, 1455, 1350, 1324, 1212, 1155, 1082, 967, 958, 773, 699, 650.

HRMS: (CI) Calcd. for $C_{20}H_{30}O_3I$ $[M+H]^+$: 445.1240, Found: 445.1247.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4
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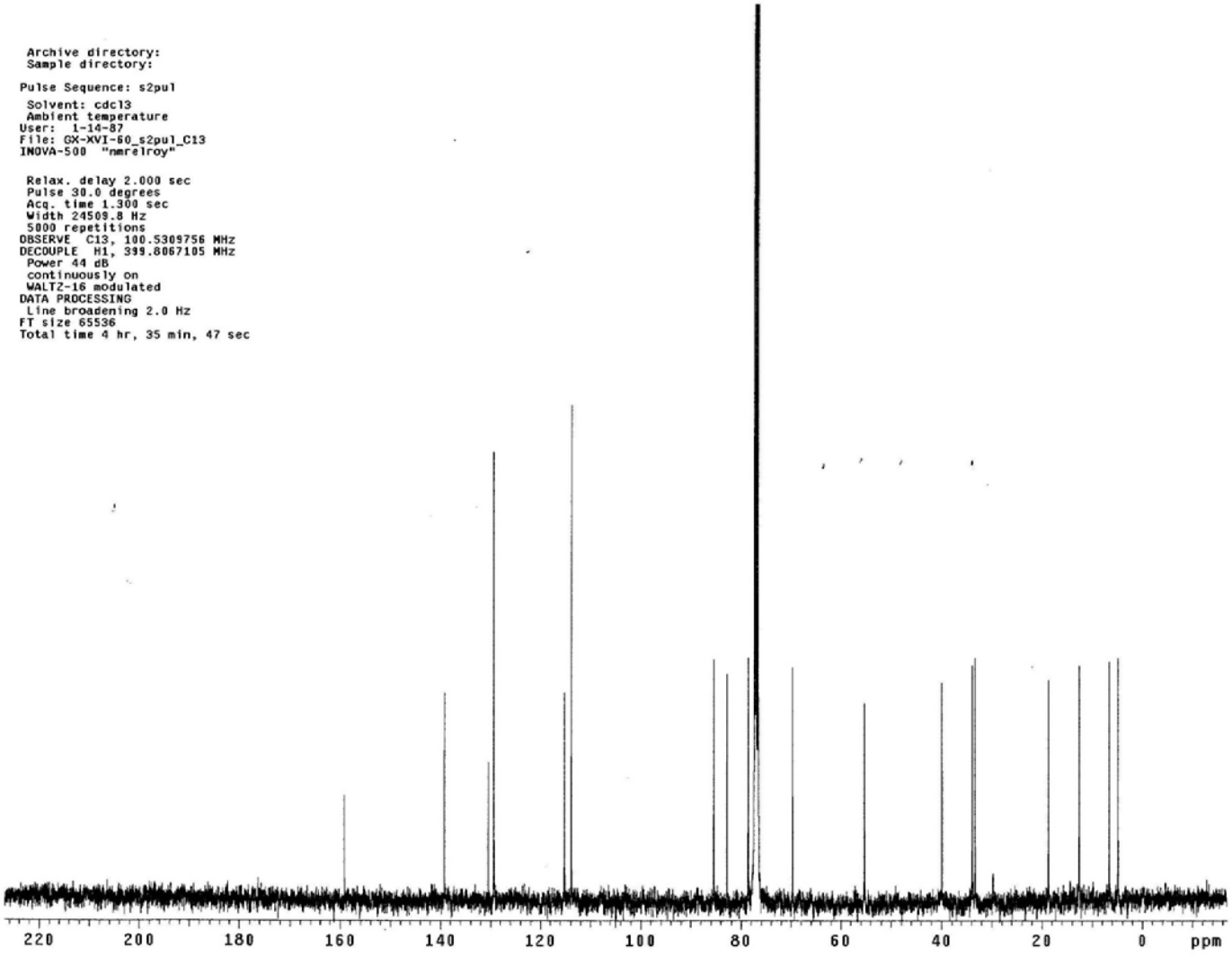
ppm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Power 44 dB
continuously on
WALTZ-16 modulated
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Line broadening 2.0 Hz
FT size 65536
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200
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160
140
120
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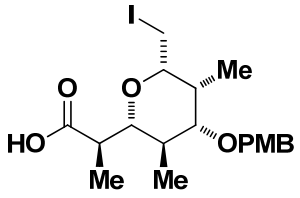
80
60
40
20
0
ppm

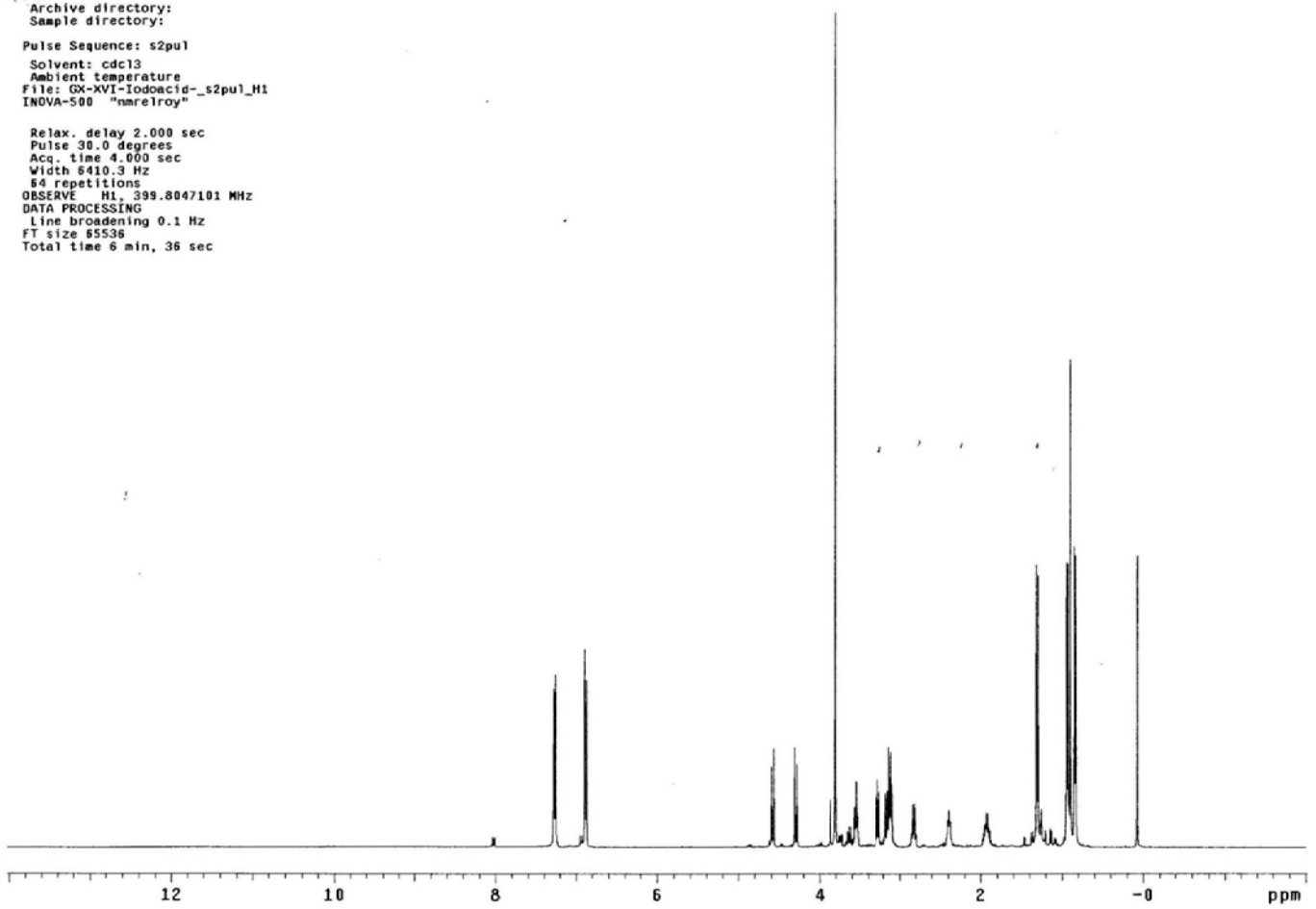
(*R*)-2-((*2R,3R,4R,5R,6S*)-6-(iodomethyl)-4-((4-methoxybenzyl)oxy)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)propanoic acid



5.8a

A solution of **5.8** in DMF (15.0 mL, 0.05 M) was added stock solution of OsO_4 in *t*-butanol (128.7 mg, 4% in H_2O, 0.02 mmol, 3 mol%). After 5 min stirring under room temperature, solid Oxone (1.660 g, 2.7 mmol, 400 mol%) was added to this solution in one portion. The reaction was stirred at room temperature for 6 hr. The reaction mixture was warmed to 0 °C and was allowed to stir at this temperature for 6 hr. Saturated aqueous $Na_2S_2O_3$ was added and the reaction mixture was stirred vigorously for 15 min. The reaction mixture was acidified with pH = 4.00 buffer solution and transferred to a separatory funnel. The aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:10) to give the title compound (274.6 mg, 0.594 mmol) as a colorless oil in 88% yield.

TLC (SiO_2): R_f = 0.39 (ethyl acetate:hexanes, 1:2).
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.28-7.26 (m, 2H), 6.89-6.87 (m, 2H), 4.58 (d, *J* = 11.2 Hz, 1H), 4.29 (d, *J* = 11.2 Hz, 1H), 3.81 (s, 3H), 3.57-3.53 (m, 1H), 3.27 (dd, *J* = 10.0, 7.6 Hz, 1H), 3.16 (dd, *J* = 10.4, 2.4 Hz, 1H), 3.13-3.09 (m, 2H), 2.82 (td, *J* = 7.2, 2.4 Hz, 1H), 2.41-2.36 (m, 1H), 1.98-1.88 (m, 1H), 1.30 (d, *J* = 7.2 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR(100 MHz, $CDCl_3$): δ 177.7, 159.2, 130.1, 129.4, 113.8, 83.7, 82.3, 79.3, 69.8, 55.3, 41.5, 33.7, 33.4, 13.9, 12.8, 5.4, 4.9.
$[\alpha]_D^{25}$ = +45.9 (c = 0.55, $CHCl_3$).
FTIR (neat): υ 3500, 3348, 3150, 3000, 2976, 2951, 1705, 1620, 1543, 1243, 1175, 1067, 922, 878, 842, 773, 692, 668.
HRMS: (CI) Calcd. for $C_{19}H_{28}O_5I$ $[M+H]^+$: 463.0982, Found: 463.0981.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64 repetitions
OBSERVE H1, 399.8047101 MHz
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Total time 6 min, 36 sec
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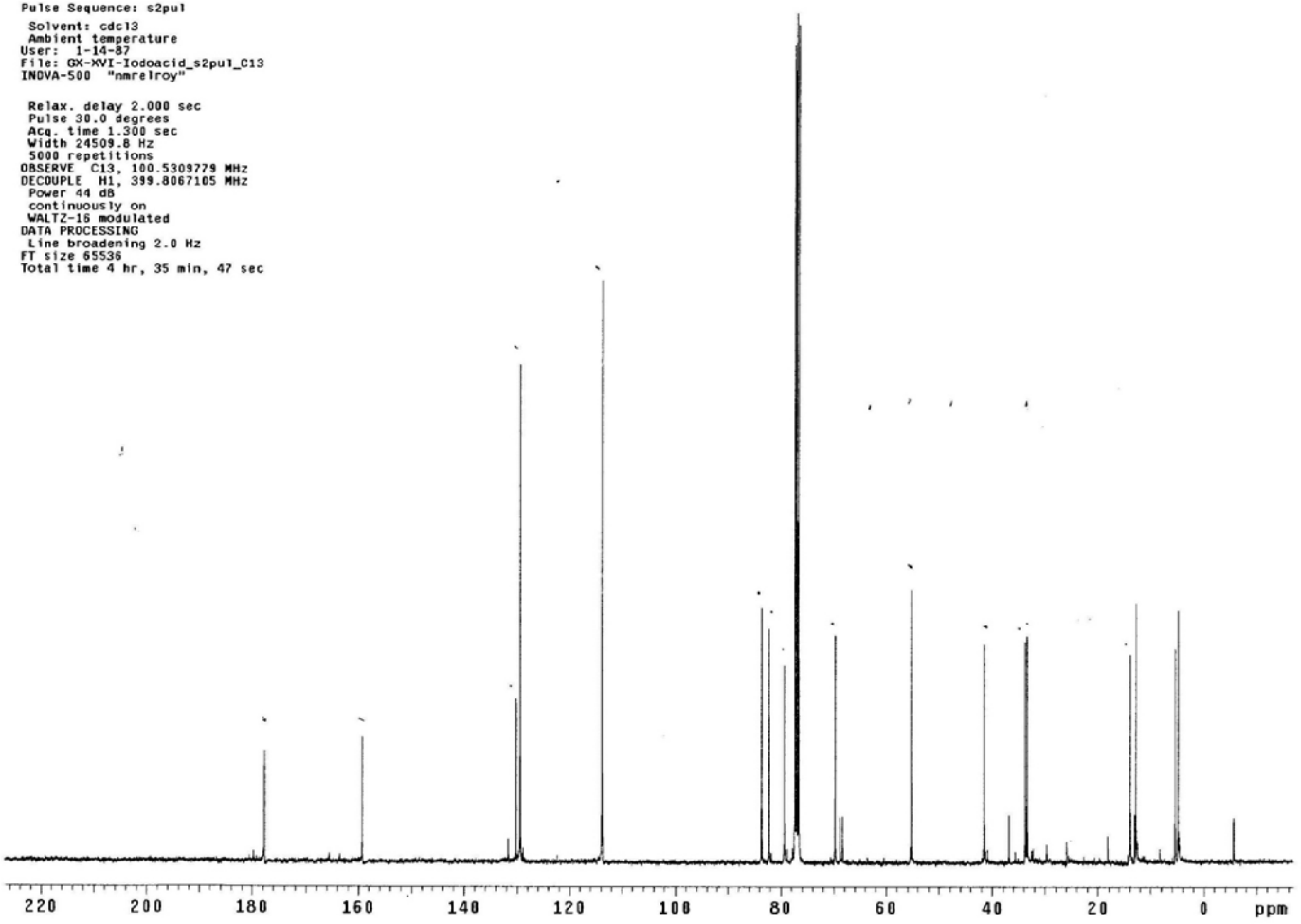
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Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309779 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
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200
180
160
140
120
100
80
60
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20
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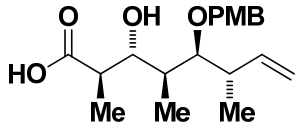
ppm

(*2R,3R,4S,5S,6S*)-3-hydroxy-5-((4-methoxybenzyl)oxy)-2,4,6-trimethyloct-7-enoic acid



5.9

A solution of (*R*)-2-((*2R,3R,4R,5R,6S*)-6-(iodomethyl)-4-((4-methoxybenzyl)oxy)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)propanoic acid (137.1 mg, 0.297 mmol, 100 mol%) in EtOH (3 mL, 0.1 M) was added activated Zn (289.6 mg, 4.455 mmol, 1500 mol%) and NH_4Cl (158.9 mg, 2.97 mmol, 1000 mol%). The reaction mixture was heated under refluxing for 1 hr. The crude reaction mixture was diluted with ethyl acetate (15 mL) and HCl in THF (1 mL, 1.0M) and filtered through a silica plug. The filtrate was concentrated under reduced pressure. Purification by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:3) gave the title compound (91.9 mg, 0.273 mmol) as a colorless oil in 92% yield.

TLC (SiO_2): R_f = 0.45 (methanol:DCM, 1:9).

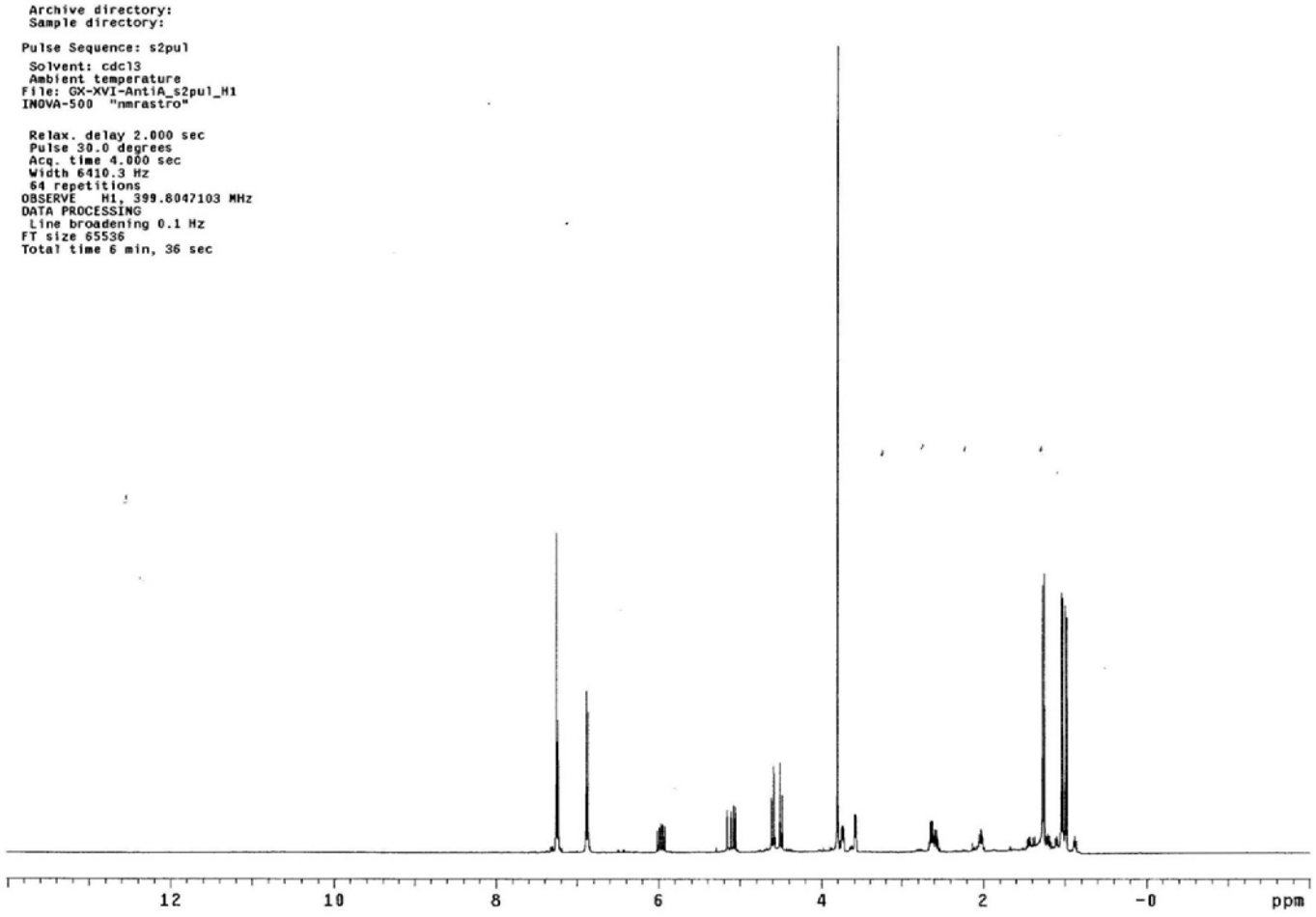
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.26-7.24 (m, 2H), 6.89-6.87 (m, 2H), 5.97 (ddd, *J* = 17.2, 10.0, 8.0 Hz, 1H), 5.14 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.07 (dd, *J* = 10.0, 1.6 Hz, 1H), 4.60 (d, *J* = 10.8 Hz, 1H), 4.49 (d, *J* = 10.8 Hz, 1H), 3.80 (s, 3H), 3.74 (dd, *J* = 8.0, 4.8 Hz, 1H), 3.58 (dd, *J* = 6.0, 2.8 Hz, 1H), 2.67-2.53 (m, 2H), 2.08-1.99 (m, 1H), 1.27 (d, *J* = 7.2 Hz, 3H), 1.03 (d, *J* = 7.2 Hz, 3H), 1.00 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 177.4, 159.5, 141.0, 129.8, 129.6, 115.2, 114.0, 84.0, 76.3, 73.1, 55.3, 42.4, 40.1, 37.1, 18.3, 14.8, 12.2.

$[\alpha]_D^{25}$ = -21.7 (c = 0.58, $CHCl_3$).

FTIR (neat): υ3500, 3428, 3050, 3044, 2984, 2941, 1705, 1616, 1533, 1249, 1170, 1060, 922, 878, 842.

HRMS: (CI) Calcd. for $C_{19}H_{29}O_5$ $[M+H]^+$: 337.2015, Found: 337.2020.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Acq. time 4.000 sec
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64 repetitions
OBSERVE H1, 399.8047103 MHz
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Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
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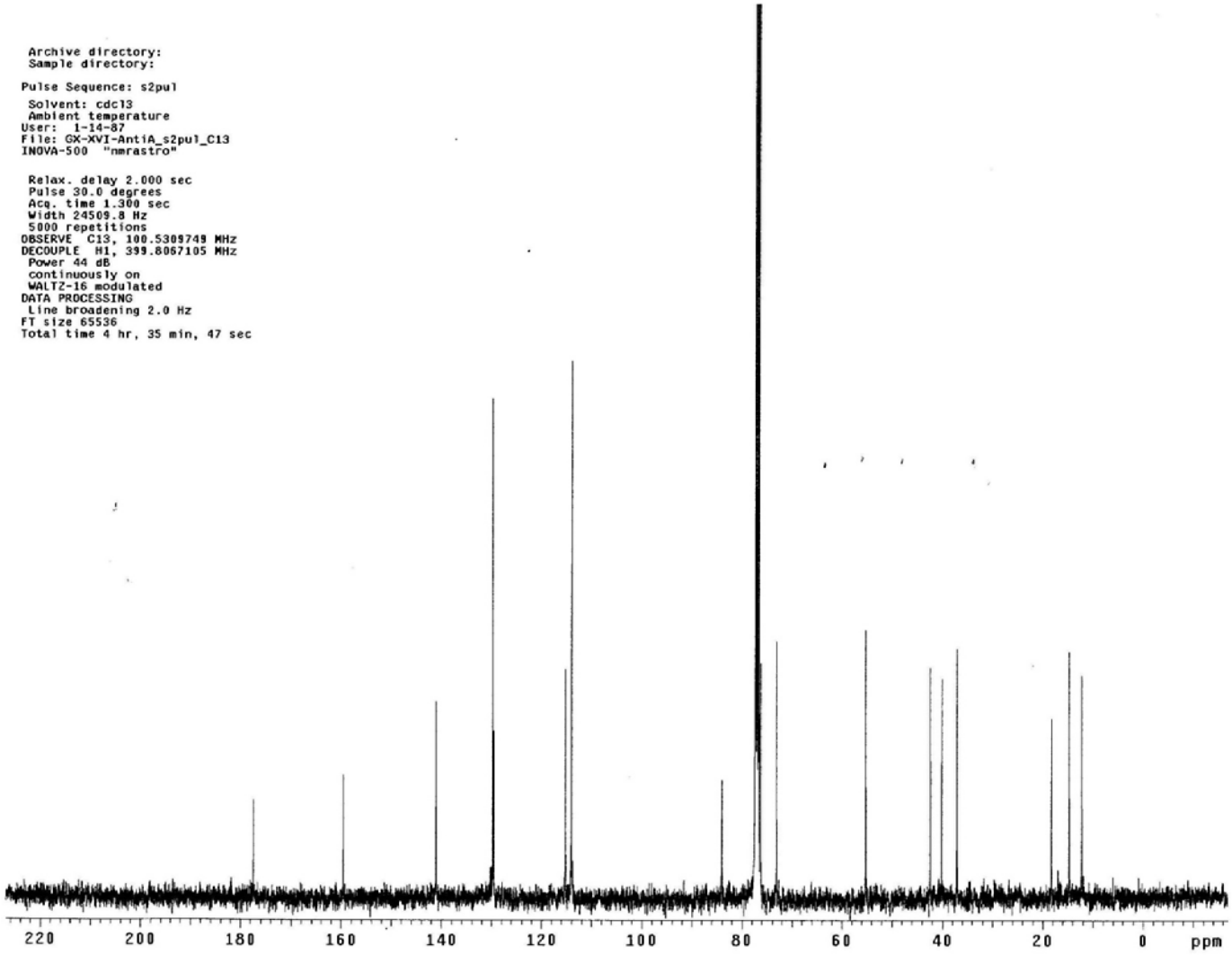
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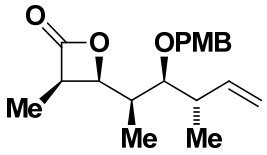
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309749 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

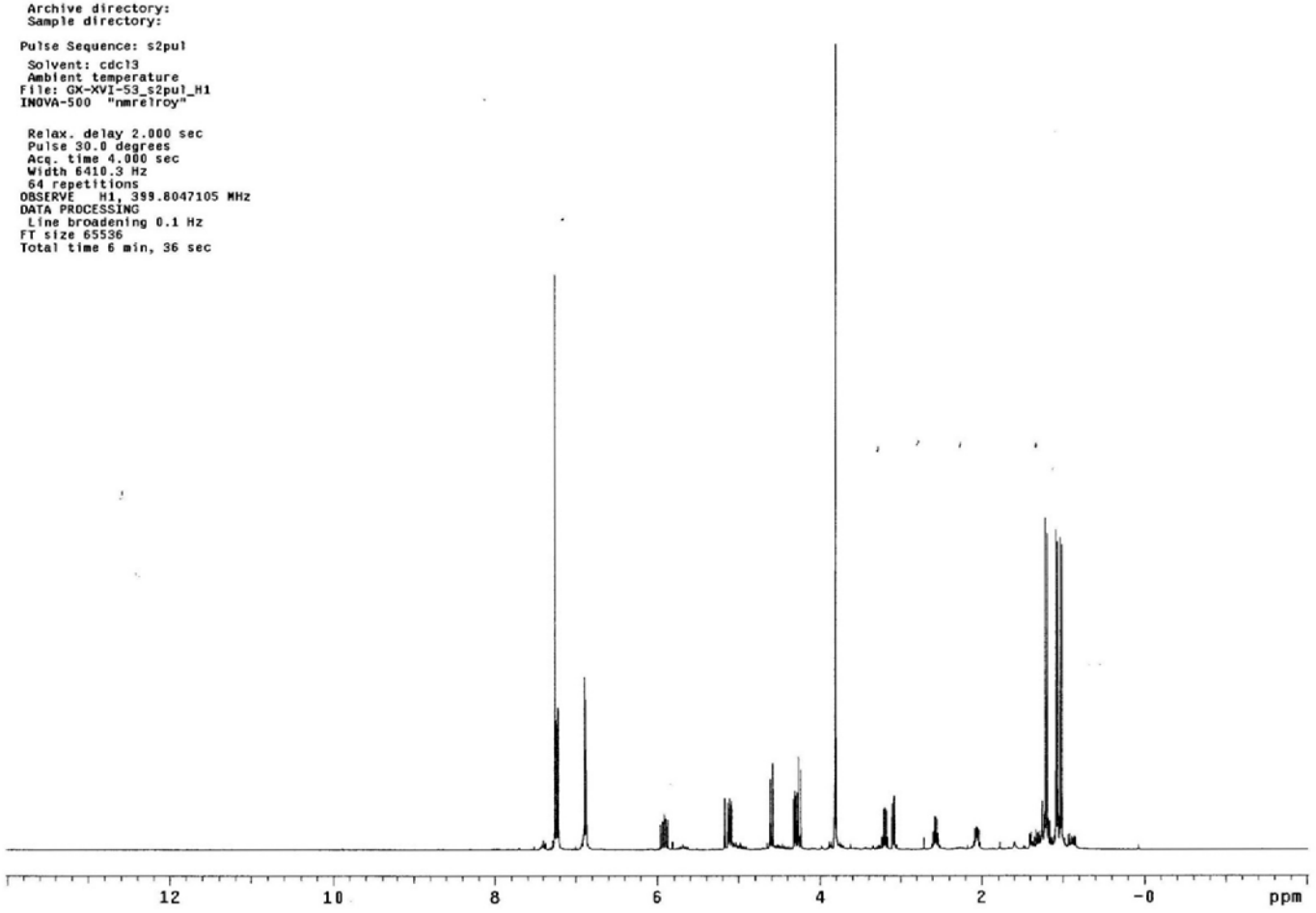
(*3R,4S*)-4-((*2R,3S,4S*)-3-((4-methoxybenzyl)oxy)-4-methylhex-5-en-2-yl)-3-methyloxetan-2-one



5.10

A solution of **5.9** (34 mg, 0.1 mmol, 100 mol%) in THF:HMPA (0.5, 1:1, 0.20 M) was cooled to -78 °C. To this solution was added *s*-butyl lithium (0.26 mL, 1.4 M, 0.35 mmol, 350 mol%) dropwise. The reaction was warmed to -20 °C and stirred for 2 hr. Chloromethanesulfonyl chloride (52.2 mg, 0.35 mmol, 350 mol%) in THF (0.1 mL) was added to the reaction mixture and stirring was continued for another 2 hr. Pyridine:H_2O (15 mL, 40:1) was added and the reaction mixture was allowed to stir under 35 °C overnight. The reaction mixture was diluted with ethyl acetate (100 mL) and transferred to a separatory funnel. The organic phase was washed with $CuSO_4$ (30 mL), water (30 mL) and brine (30 mL). The organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:20) to give the title compound (22.9 mg, 0.072 mmol) as a colorless oil in 72% yield.

TLC (SiO_2): R_f = 0.73 (ethyl acetate:hexanes, 1:2).
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.24-7.22 (m, 2H), 6.89-6.87 (m, 2H), 5.91 (ddd, *J* = 18.0, 10.4, 8.0 Hz, 1H), 5.15 (dd, *J* = 18.0, 1.2 Hz, 1H), 5.09 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.60 (d, *J* = 11.6 Hz, 1H), 4.30 (dd, *J* = 10.8, 6.4 Hz, 1H), 4.25 (d, *J* = 11.6 Hz, 1H), 3.81 (s, 3H), 3.19 (qd, *J* = 8.0, 6.0 Hz, 1H), 3.08 (dd, *J* = 8.0, 1.6 Hz, 1H), 2.56 (qd, *J* = 14.8, 6.8 Hz, 1H), 2.06 (dqd, *J* = 13.6, 6.8, 1.6 Hz, 1H), 1.20 (d, *J* = 8.0 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR(100 MHz, $CDCl_3$): δ 172.7, 159.4, 141.2, 130.1, 129.9, 115.2, 113.8, 80.4, 77.6, 73.3, 55.3, 46.4, 41.0, 35.6, 16.7, 9.4, 9.0.
$[\alpha]_D^{25}$ = -20.1 (c = 0.34, $CHCl_3$).
FTIR (neat): υ3300, 3080, 2963, 2925, 1821, 1466, 1377, 1128, 1043, 1000, 970, 923, 888, 842, 761, 731.
HRMS: (CI) Calcd. for $C_{19}H_{26}O_4$ $[M]^+$: 316.1675, Found: 316.1673.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64 repetitions
OBSERVE H1, 399.8047105 MHz
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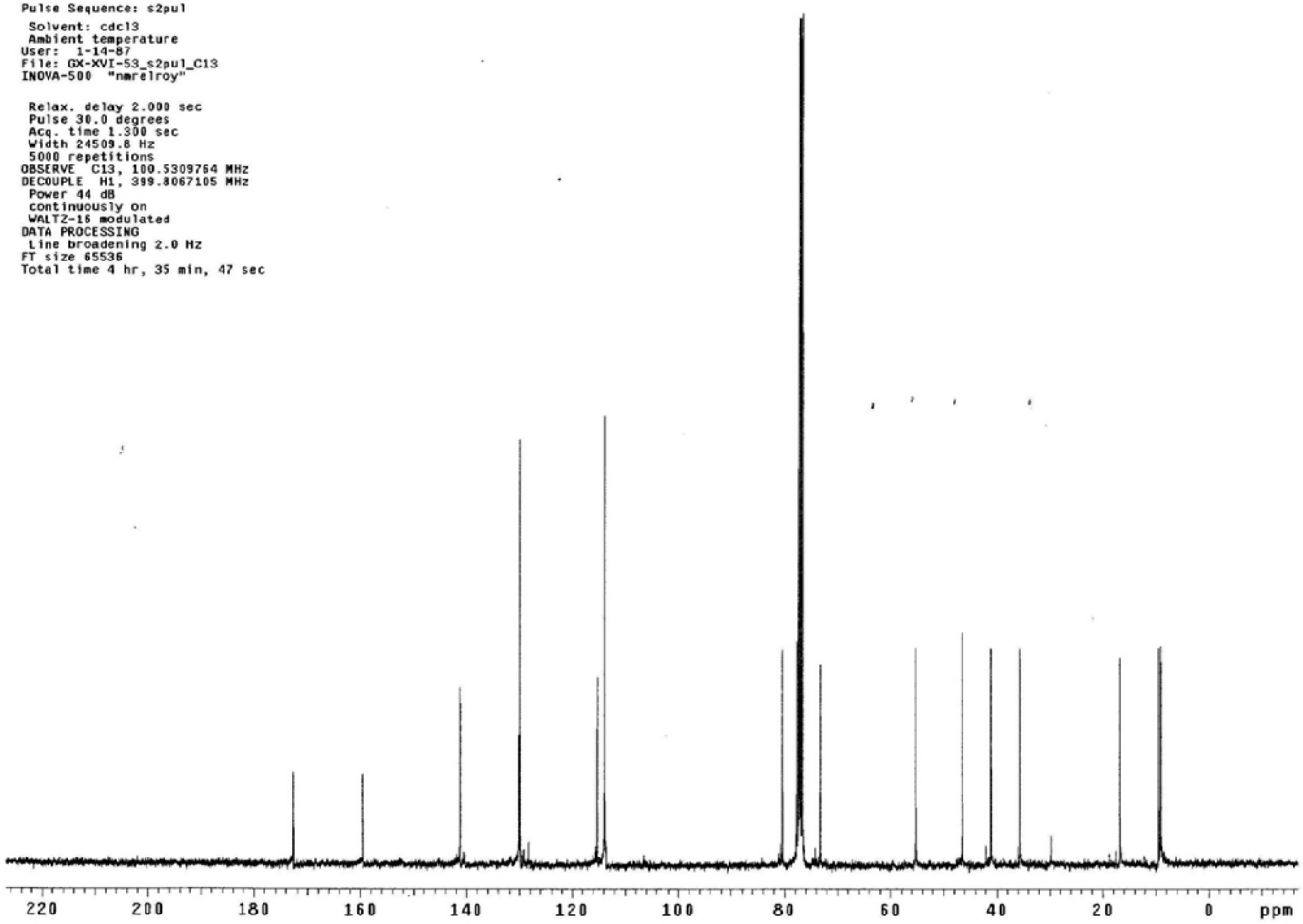
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Ambient temperature
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Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309764 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
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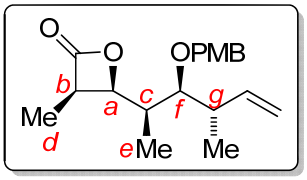
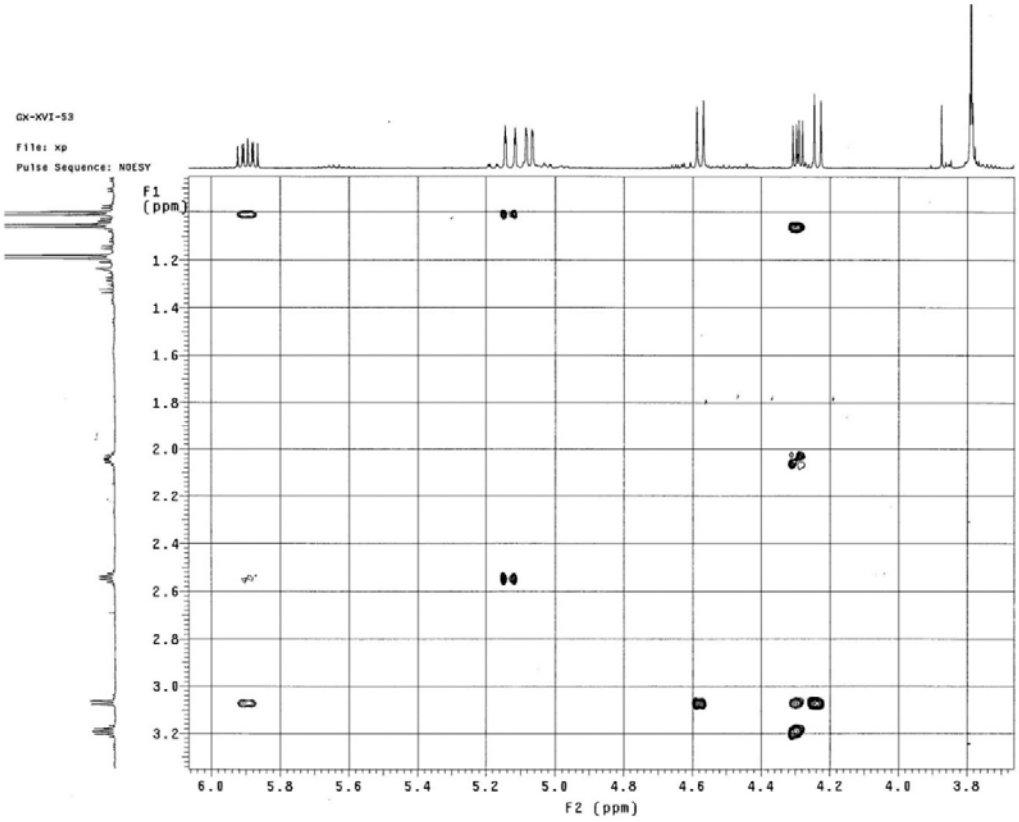
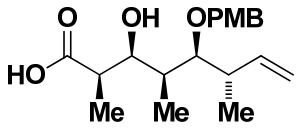




The NOE experiment shows clearly the NOE interaction between [a]H and [b]H, while [a]H and [d]H shows no NOE interaction towards each other. This data suggest a *syn* relationship of stereochemistry across the lactone ring.

(*2R,3S,4S,5S,6S*)-3-hydroxy-5-((4-methoxybenzyl)oxy)-2,4,6-trimethyloct-7-enoic acid



5.10a

A solution of (*3R,4S*)-4-((*2R,3S,4S*)-3-((4-methoxybenzyl)oxy)-4-methylhex-5-en-2-yl)-3-methyloxetan-2-one (200 mg, 0.63 mmol, 100 mol%) in dioxane:H_2O (12.6 mL, 1:1, 0.05 M) was added LiOH monohydrate (52.9 mg, 1.26 mmol, 200 mol%) in one portion. The reaction was stirred overnight. pH = 4 buffer solution (15 mL) was added and the reaction mixture was transferred to a separatory funnel. The aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:3) to give the title compound (148.4 mg, 0.441 mmol) as a colorless oil in 70% yield.

TLC (SiO_2): R_f = 0.32 (ethyl acetate:hexanes, 1:1).

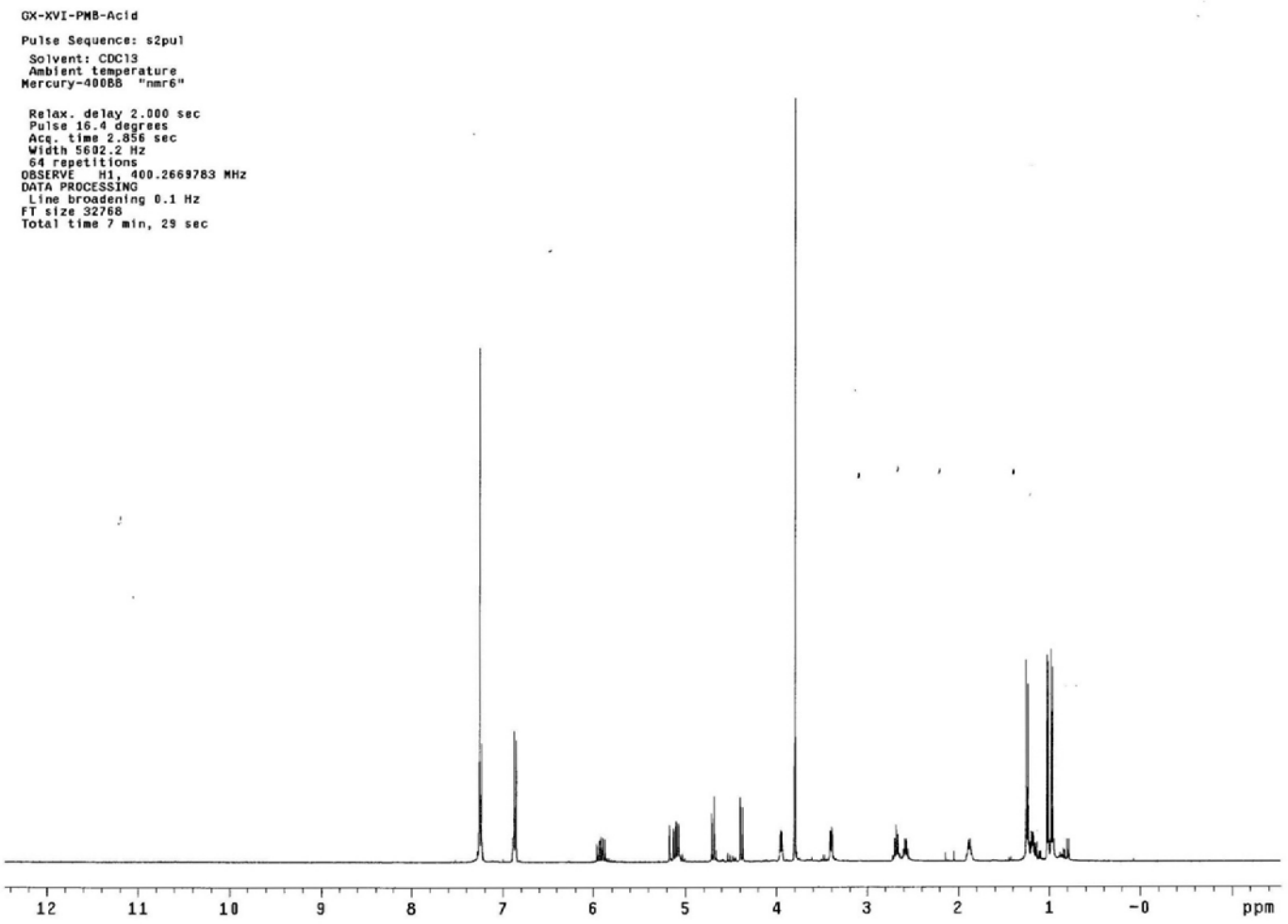
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.26-7.24 (m, 2H), 6.89-6.86 (m, 2H), 5.92 (ddd, *J* = 17.6, 10.4, 8.4 Hz, 1H), 5.15 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.08 (ddd, *J* = 10.4, 2.0, 0.8 Hz, 1H), 4.70 (d, *J* = 10.4 Hz, 1H), 4.38 (d, *J* = 10.4 Hz, 1H), 3.95 (dd, *J* = 7.6, 2.0 Hz, 1H), 3.80 (s, 3H), 3.40 (dd, *J* = 7.6, 3.2 Hz, 1H), 2.72-2.65 (m, 1H), 2.62-2.53 (m, 1H), 1.88 (qdd, *J* = 8.4, 7.2, 4.0 Hz, 1H), 1.24 (d, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 178.6, 159.4, 141.3, 129.8, 129.6, 115.2, 113.9, 87.5, 76.0, 73.6, 55.3, 42.6, 41.1, 36.6, 16.9, 13.2, 6.9.

$[\alpha]_D^{25}$ = -47.2 (c = 0.83, $CHCl_3$).

FTIR (neat): υ3478, 3409, 3081, 3068, 2974, 2938, 1707, 1613, 1514, 1459, 1249, 1175, 1035, 916, 820.

HRMS: (CI) Calcd. for $C_{19}H_{29}O_5$ $[M+H]^+$: 337.2015, Found: 337.2018.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Solvent: CDCl3
Ambient temperature
Mercury-400BB "nmr6"
Relax. delay 2.000 sec
Pulse 16.4 degrees
Acq. time 2.856 sec
Width 5602.2 Hz
64 repetitions
OBSERVE H1, 400.2669783 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 7 min, 29 sec
12
11
10
9
8
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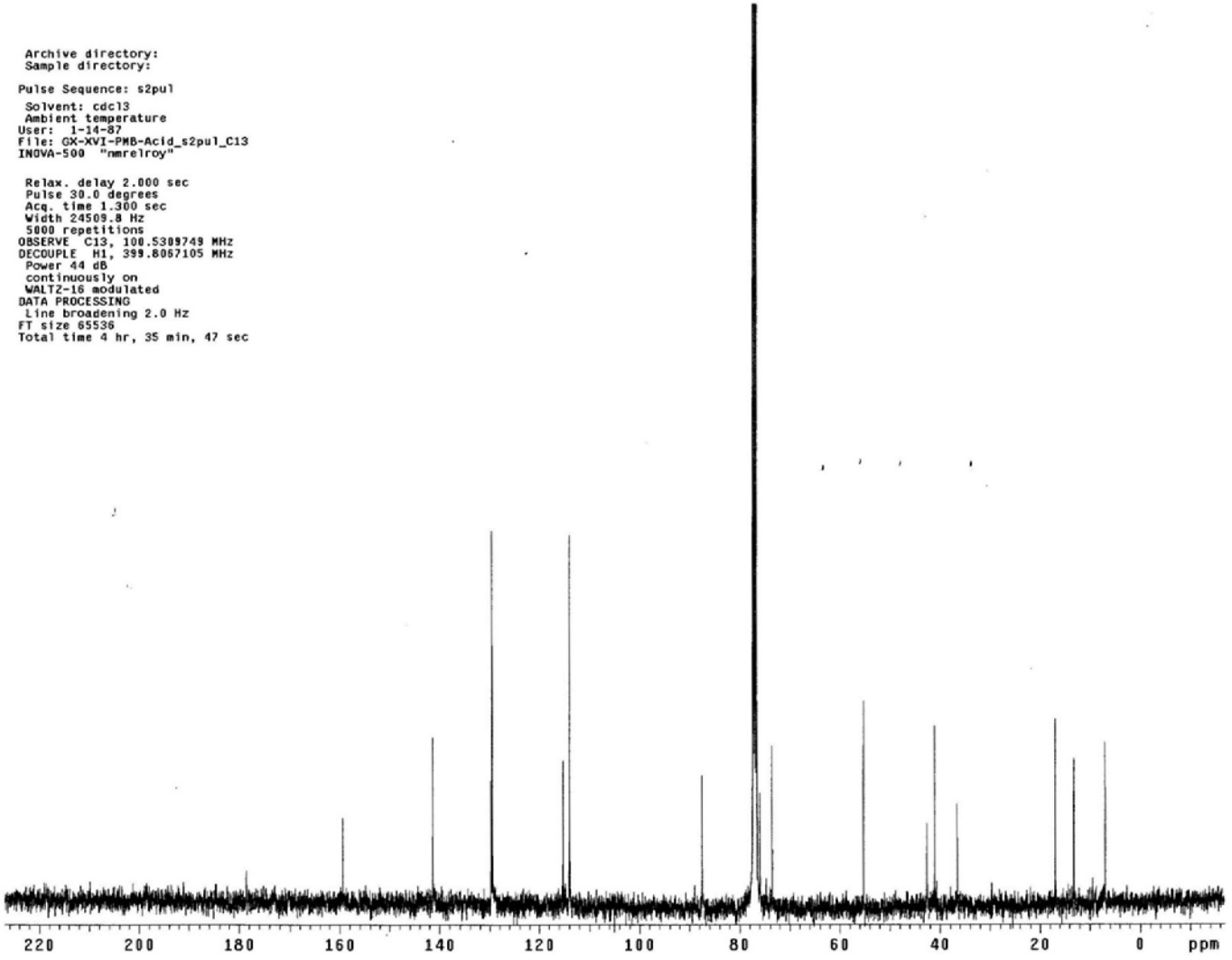
6
5
4
3
2
1
-0
ppm


Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
User: 1-14-87
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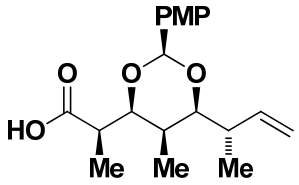
INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5389749 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(*R*)-2-((*2S,4S,5R,6S*)-6-((*S*)-but-3-en-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propanoic acid



Fragment 5B

A solution of (*2R,3S,4S,5S,6S*)-3-hydroxy-5-((4-methoxybenzyl)oxy)-2,4,6-trimethyloct-7-enoic acid (148.4 mg, 0.441 mmol, 100 mol%) and 4Å molecular sieves (480.5 mg) in DCM (8.82 mL, 0.05 M) was cooled to 0 °C. To this solution was added DDQ (120.1 mg, 0.529 mmol, 120 mol%) in three portions. The reaction was stirred at 0 °C for 1 hr. The reaction mixture was loaded on to the column directly. Purification by column chromatography (SiO_2; ethyl acetate: hexanes, 1:3) gave the title compound (118.0 mg, 0.353 mmol) as a colorless oil in 80% yield.

TLC (SiO_2): R_f = 0.69 (ethyl acetate:hexanes, 1:1).

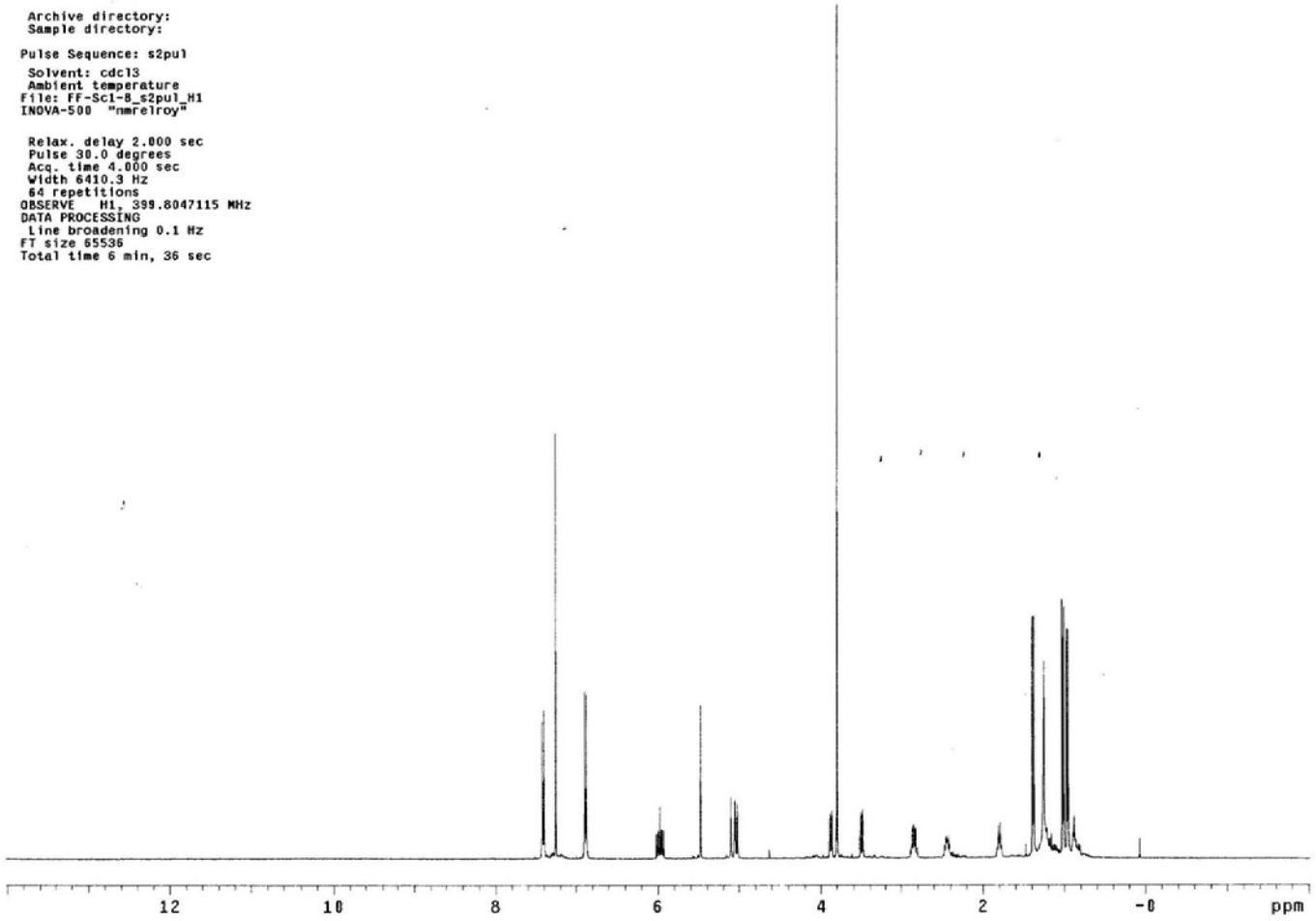
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.42-7.40 (m, 2H), 6.90-6.88 (m, 2H), 5.97 (ddd, *J* = 17.2, 10.4, 6.4 Hz, 1H), 5.48 (s, 1H), 5.08 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.03 (dt, *J* = 10.4, 1.6 Hz, 1H), 3.88 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.80 (s, 3H), 3.50 (dd, *J* = 10.0, 2.0 Hz, 1H), 2.85 (qdd, *J* = 6.8, 6.4, 2.0 Hz, 1H), 2.44 (qd, *J* = 6.8, 3.2 Hz, 1H), 1.80 (qd, *J* = 6.8, 2.0 Hz, 1H), 1.38 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 178.7, 159.9, 141.6, 131.1, 127.2, 114.0, 113.5, 101.3, 84.5, 81.8, 55.3, 41.7, 38.3, 29.7, 14.9, 14.3, 6.0.

$[\alpha]_D^{25}$ = -90.2 (c = 0.36, CH_2Cl_2).

FTIR (neat): υ3334, 3255, 2970, 2922, 2852, 1737, 1645, 1557, 1517, 1375, 1302, 1170, 1132, 1104, 1033, 1011, 976, 914, 828, 668.

HRMS: (CI) Calcd. for $C_{19}H_{27}O_5$ $[M+H]^+$: 335.1859, Found: 335.1855.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Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047115 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
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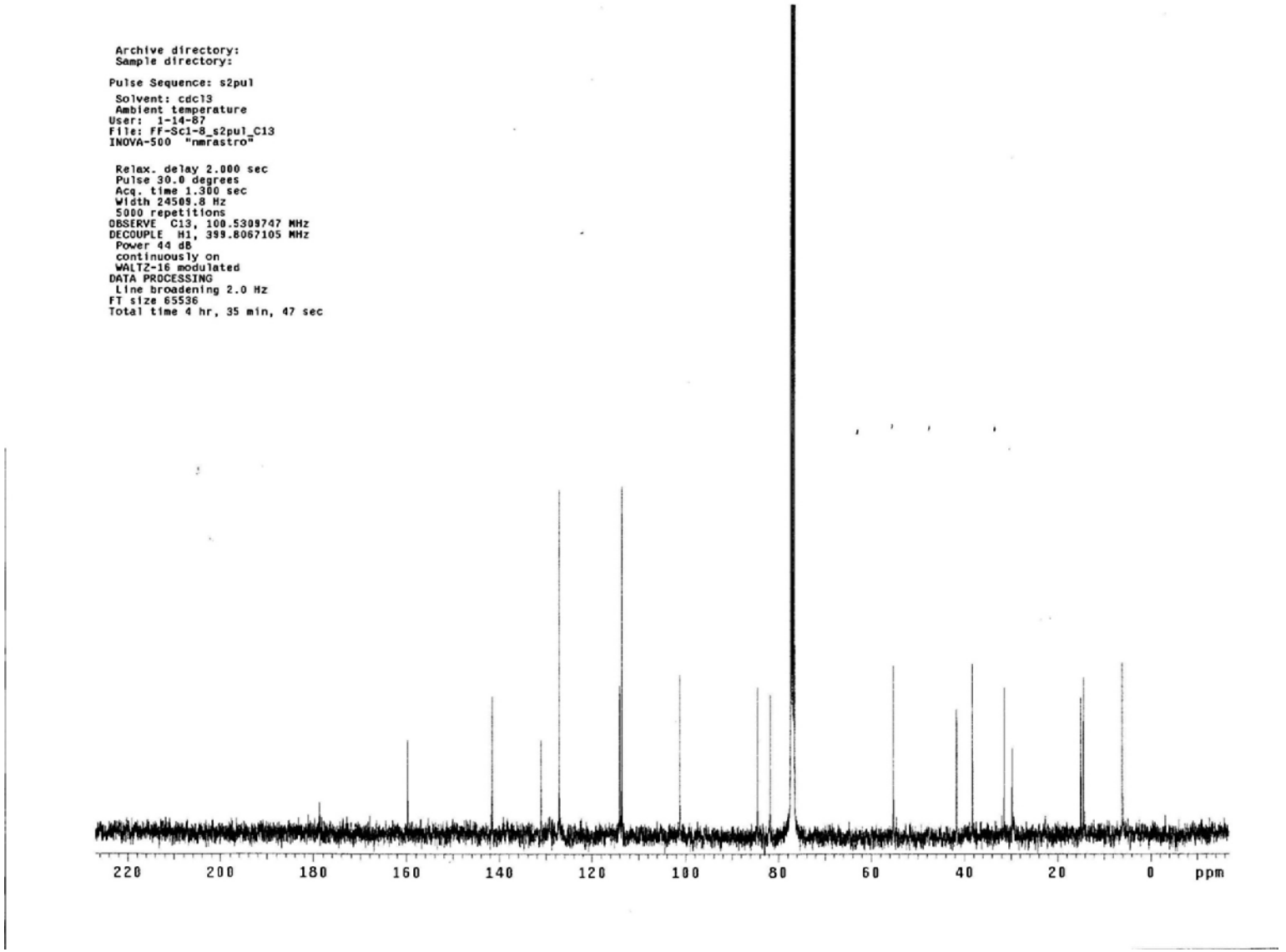
6
4
2
-0
ppm


Archive directory:
Sample directory:
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Solvent: cdcl3
Ambient temperature
User: 1-14-87
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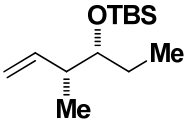
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309747 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

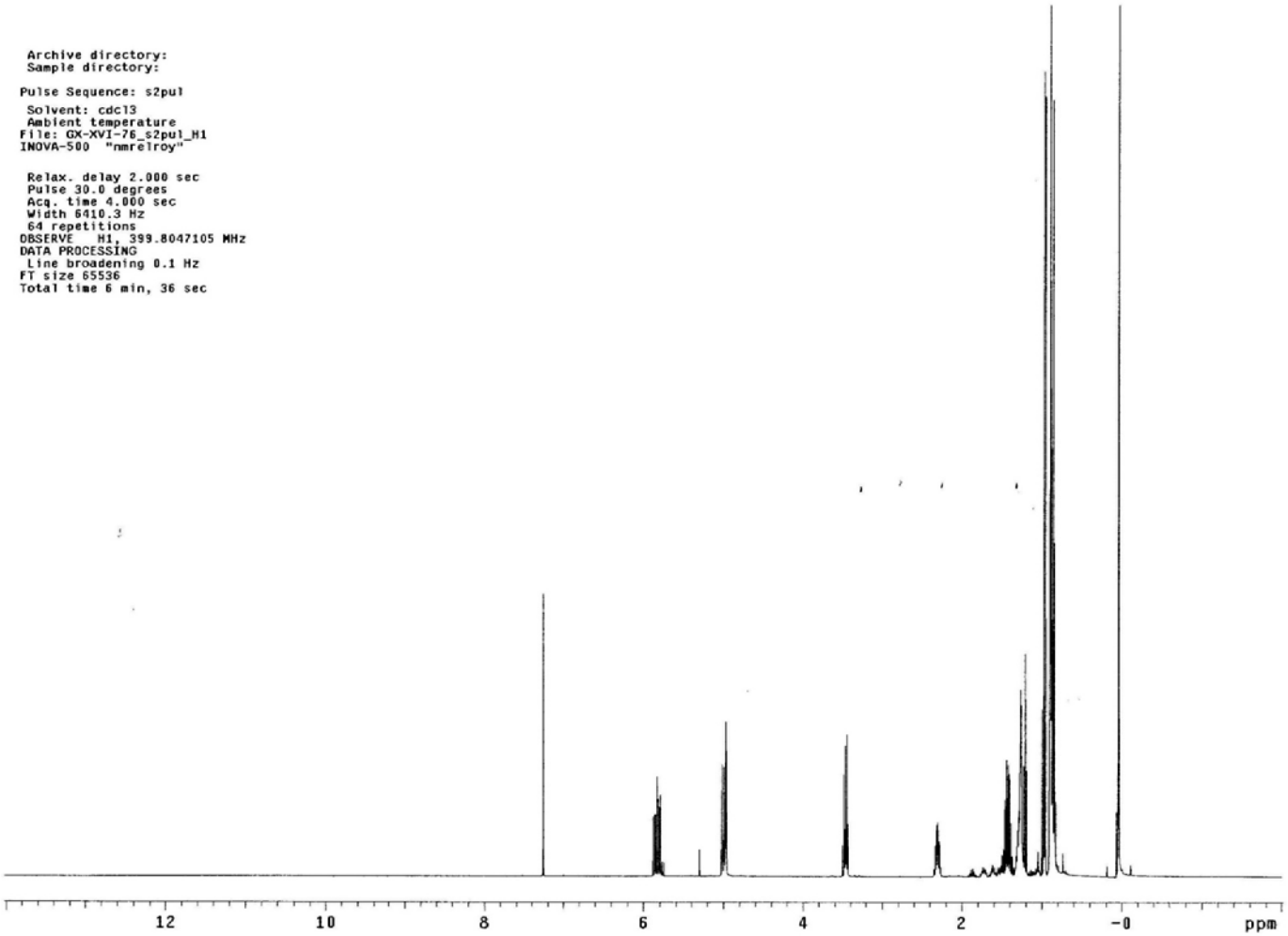
***tert*-Butyldimethyl(((*3R,4R*)-4-methylhex-5-en-3-yl)oxy)silane**



5.2

To a resealable pressure tube equipped with a magnetic stir bar was added $RuH_2(CO)(PPh_3)_3$ (321.5 mg, 0.35 mmol, 7 mol%), (*S*)-SEGPHOS (213.5 mg, 0.35 mmol, 7 mol%), TADDOL-phosphoric acid (488 mg, 0.7 mmol, 14 mol%). The tube was sealed with a rubber septum and purged with argon. Propanol (382.5 μL, 5. 0 mmol, 100 mol%) and acetone (5. 0 mL, 1.0 M concentration with respect to alcohol) were added and the solution was cooled to -78 °C. Butadiene (1.69 mL, 20.0 mmol, 400 mol%) was quickly added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 95 °C (oil bath temperature) for 3 days, at which point the reaction mixture was allowed to cool to ambient temperature. TBSCl (1.507 g, 10.0 mmol, 200 mol%) and imidazole (0.851 g, 12.5 mmol, 250 mol%) were added and the reaction mixture was diluted with DMF (25 mL) and stirred under 70 °C for another 15 hours. Aqueous $CuSO_4$ solution was added and the reaction mixture was extract with ether (20 mL × 3). Combined organic layer was dried *in vacuo* and purified by flash column chromatography (SiO_2; hexanes) to furnish the title compound (673.9 mg, 2.95 mmol, *syn*:*anti* = 4.7:1, 98% ee) as a colorless oil in 59% yield.

TLC (SiO_2): R_f = 0.64 (hexanes).
^{1}H NMR(400 MHz, $CDCl_3$): δ5.83 (ddd, *J* = 17.6, 10.4, 7.2 Hz, 1H), 5.02-4.96 (m, 2H), 3.51-3.44 (m, 1H), 2.35-2.26 (m, 1H), 1.46-1.37 (m, 2H), 0.96 (d, *J* = 7.2 Hz, 1H), 0.90 (s, 9H), 0.86 (t, *J* = 7.2 Hz, 1H), 0.04 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ141.8, 113.6, 76.7, 42.3, 26.5, 25.9, 15.0, 9.5, -4.3, -4.4.
FTIR (neat): υ2956, 2927, 1462, 1251, 771.
$[\alpha]_D^{25}$ = +20.8 (c = 1.1, CH_2Cl_2).
HPLC Enantiomeric excess was determined by HPLC analysis of the 4-nitrobenzoate derivative of the product (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 0.5 mL/min, 254 nm), t_{major} = 55.3 min, t_{minor} = 66.0 min; ee = 98%.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Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047105 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
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6
4
2
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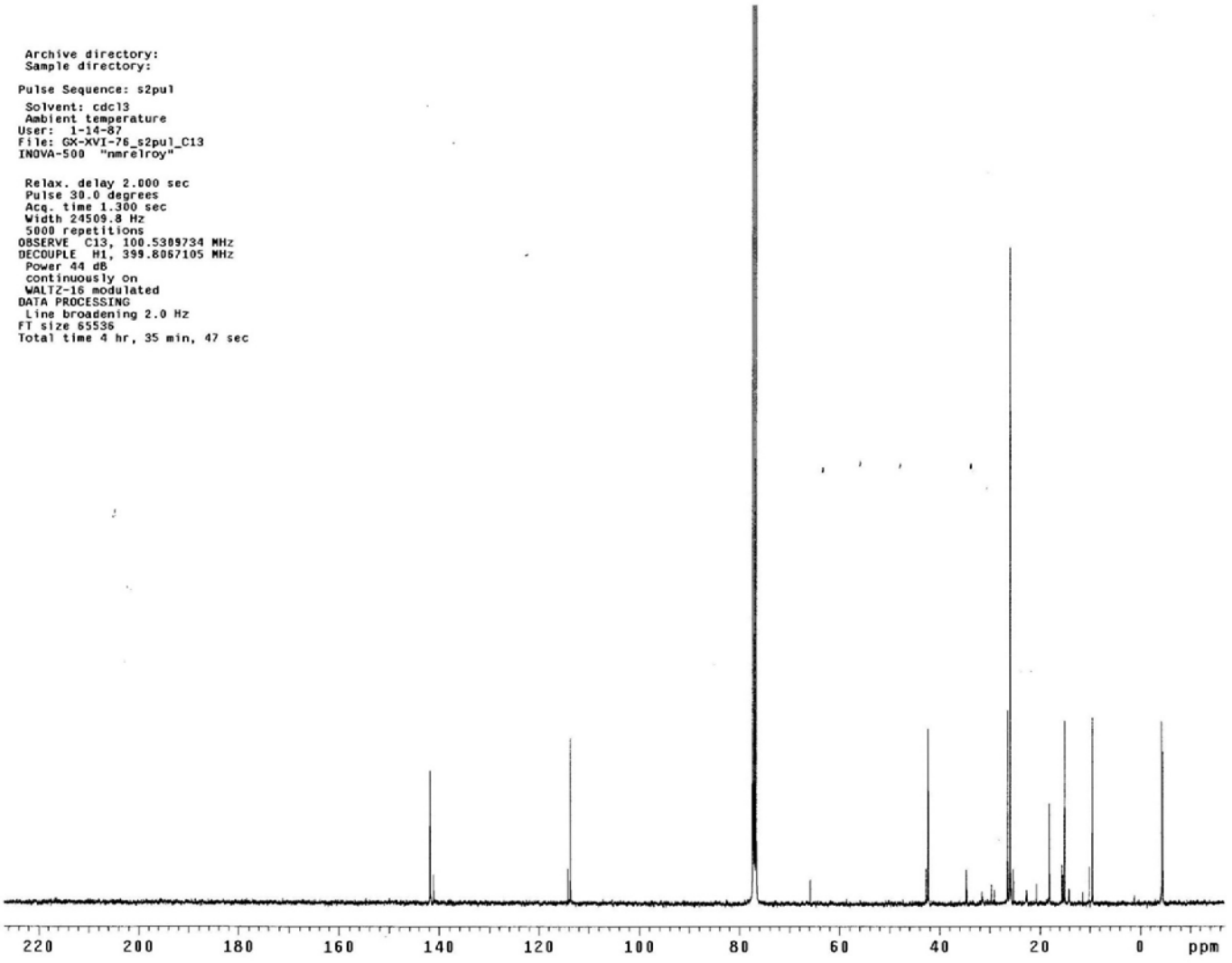
ppm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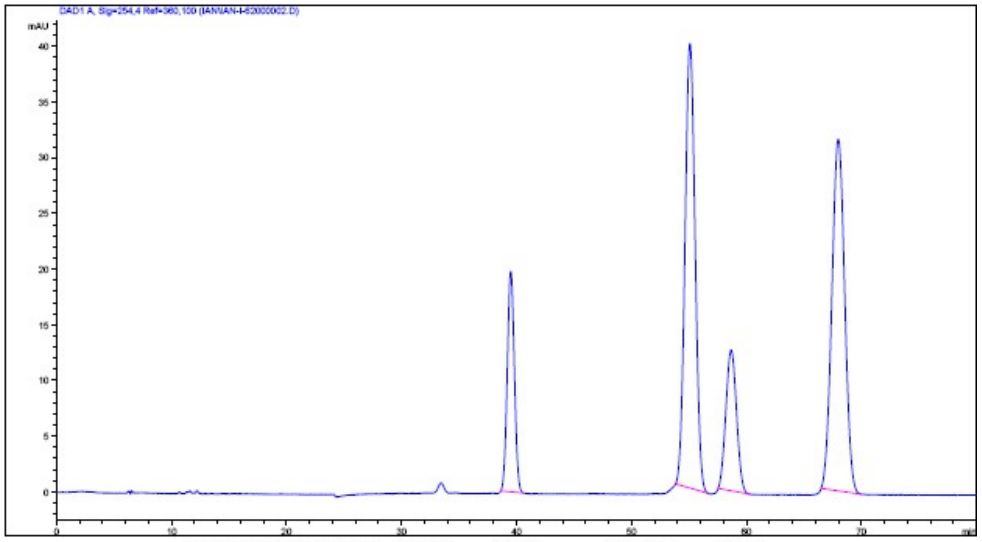
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
User: 1-14-87
File: GX-XVI-76_s2pul_C13
INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5389734 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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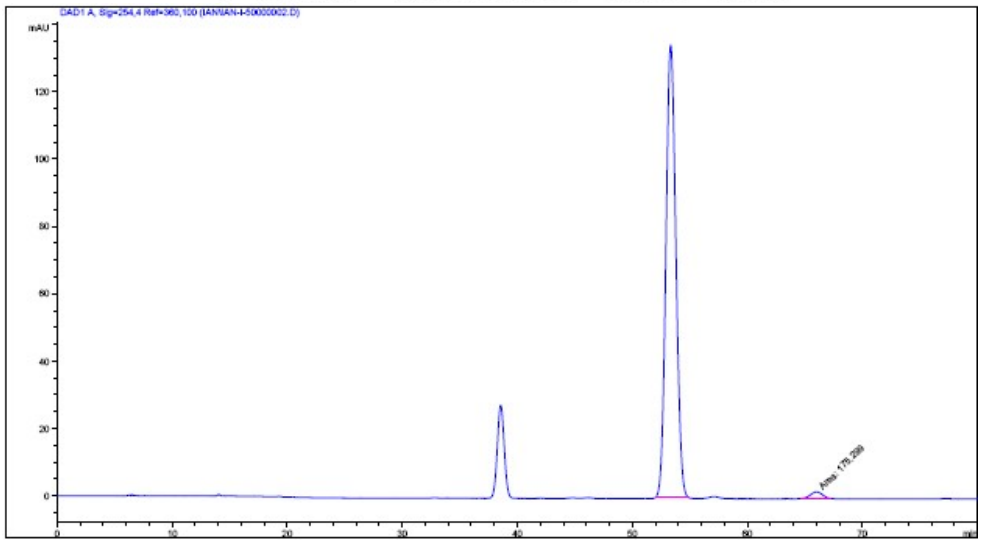
2	55.079	BB	0.9157	2436.11816	39.93385	37.2632
3	58.665	BB	0.8004	813.51562	12.64772	12.4437
4	67.979	BB	1.0884	2437.29663	31.58078	37.2813



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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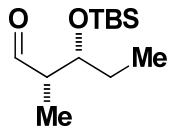
2	66.037	MM	1.3160	175.29871	2.22011	1.1229

(*2S,3R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpentanal



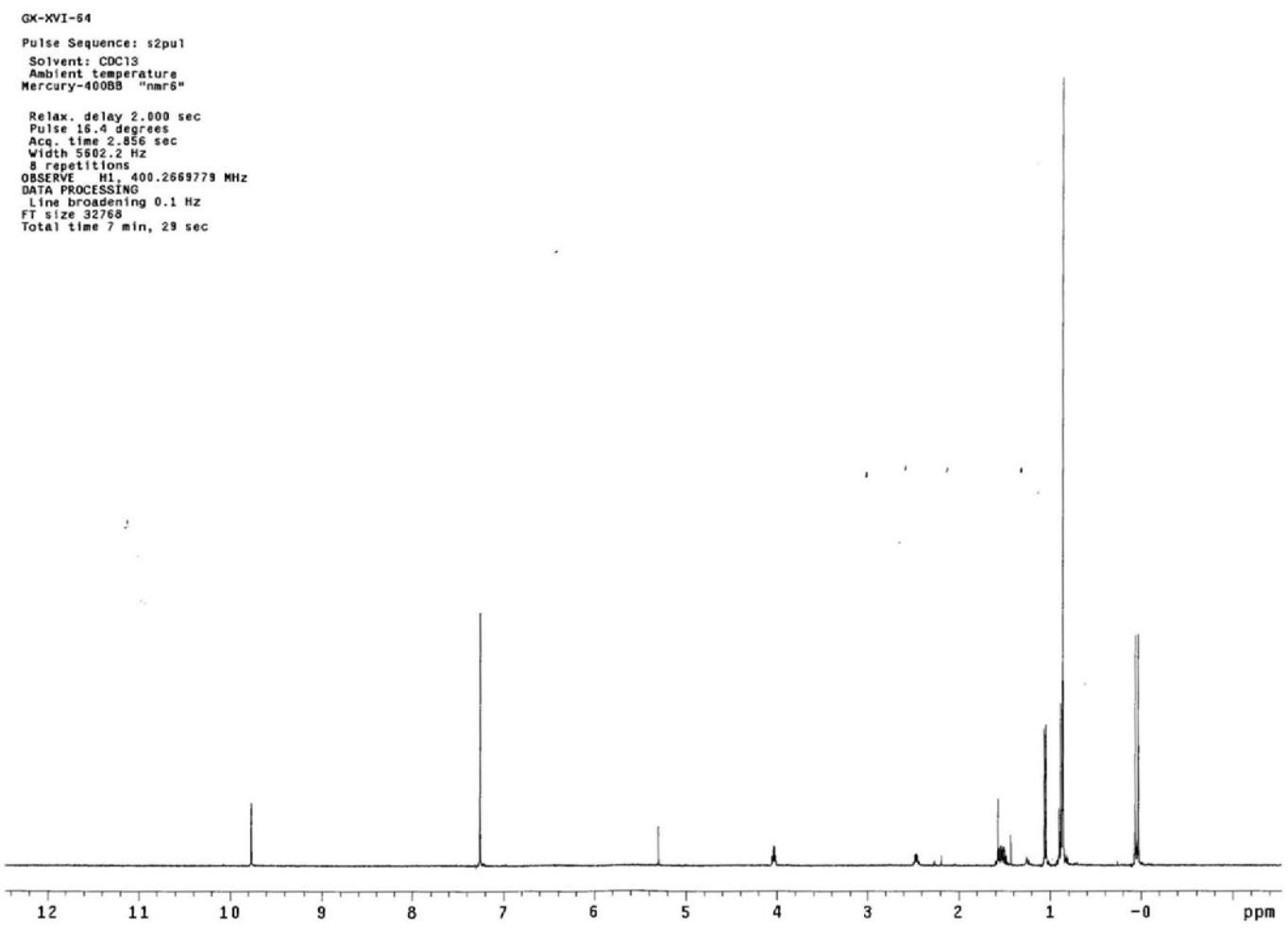
5.2a

An oven-dried round bottom flask under an atmosphere of N_2 was charged with *tert*-Butyldimethyl(((*3R,4R*)-4-methylhex-5-en-3-yl)oxy)silane (290 mg, 1.27 mmol, 100 mol%), 2,6-lutidine (271.9 mg, 2.54 mmol, 200 mol%), and THF:H_2O (12.7 mL, 3:1, 0.1 M). OsO_4 in *t*-butanol (0.76 mL, 0.05M, 0.038 mmol, 3 mol%) was added under 0 ^oC. After being stirring for 5 min, solid $NaIO_4$ (542.9 mg, 2.54 mmol, 200 mol%) was added in one portion. Stirring was continued for another 12 hr fallowed by saturated aqueous $Na_2S_2O_3$ (20 mL) was added. The reaction mixture was stirred vigorously for 15 min and then transferred to a separatory funnel. The aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was run through a silica plug to give the title compound (262 mg, 0.977 mmol) as a colorless oil in 77% yield and used in the next step without further purification.

TLC (SiO_2): R_f = 0.63 (hexanes:ethyl acetate, 10:1).

^{1}H NMR(400 MHz, $CDCl_3$): δ 9.77 (d, *J* = 0.8 Hz, 1H), 4.03 (ddd, *J* = 10.4, 7.2, 3.6 Hz, 1H), 2.47 (qdd, *J* = 7.2, 3.6, 0.8 Hz, 1H), 1.60-1.47 (m, 3H), 1.05 (d, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).

FTIR (neat): υ2980, 2977, 2962, 1710, 1458, 1231, 998, 960, 822, 771, 654.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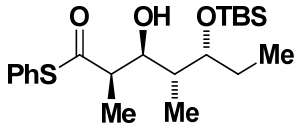
Solvent: CDCl3
Ambient temperature
Mercury-400BB "nmr6"
Relax. delay 2.000 sec
Pulse 16.4 degrees
Acq. time 2.856 sec
Width 5602.2 Hz
8 repetitions
OBSERVE H1, 400.2669779 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 7 min, 29 sec
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm

(*2R,3S,4R,5R*)-*S*-phenyl-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2,4-dimethylheptanethioate



5.3

An oven-dried round bottom flask under an atmosphere of N_2 was charged with *S*-phenyl propanethioate (170 mg, 1.0 mmol, 150 mol%) and ether (0.5 mL). 9-BBNOTf solution (2.0 mL, 0.5 M, 150 mol%) was added under 0 ^oC followed by triethylamine (0.186 mL, 1.2 mmol, 180 mol%). The bright yellow reaction mixture was stirred under room temperature for 30 min, and then cooled to -78 ^oC. (*2S,3R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpentanal (154 mg, 0.67 mmol, 100 mol%) in ether (0.5 mL, 0.7 M) was added to the reaction mixture. Stirring was continued for 1 hr then pH = 7 buffer (2 mL) was added. The layer was separated and the aqueous layer was extract with DCM (10 mL × 3). Combined organic layer was dried *in vacuo* and purified by flash column chromatography (SiO_2; hexanes:ether = 11:1-8:1) to furnish the title compound (207.3 mg, 0.52 mmol) as a colorless oil in 78% yield.

TLC (SiO_2): R_f = 0.42 (ethyl acetate:hexanes, 1:9).

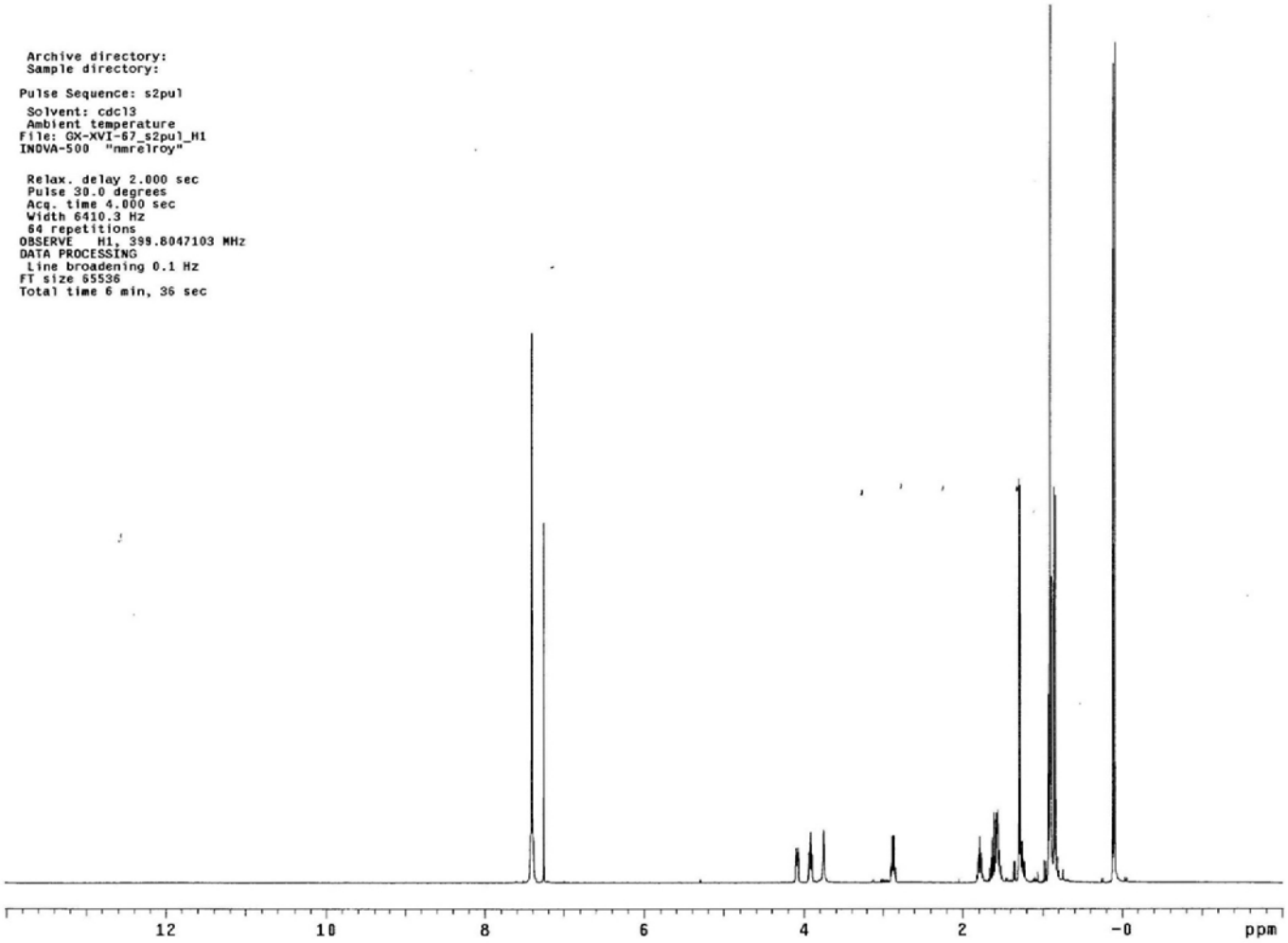
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.43-7.39 (m, 5H), 4.10-4.08 (m, 1H), 3.94-3.90 (m, 1H), 3.76 (br, 1H), 2.87 (qd, *J* = 7.8, 3.2 Hz, 1H), 1.83-1.75 (m. 1H), 1.66-1.51 (m, 3H), 1.28 (d, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 6.4 Hz, 3H), 0.90 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 201.2, 134.6, 129.3, 129.1, 127.6, 76.5, 74.2, 51.1, 38.7, 25.9, 25.8, 18.0, 11.5, 10.9, 10.2, -4.2, -4.5.

$[\alpha]_D^{25}$ = -28.8 (c = 0.55, CH_2Cl_2).

FTIR (neat): υ2928, 2858, 1714, 1457, 1252, 1217, 1003, 954, 834, 774, 744, 688, 668.

HRMS: (CI) Calcd. for $C_{21}H_{37}O_3SSi$ $[M+H]^+$: 397.3320, Found: 397.3318.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Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047103 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
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6
4
2
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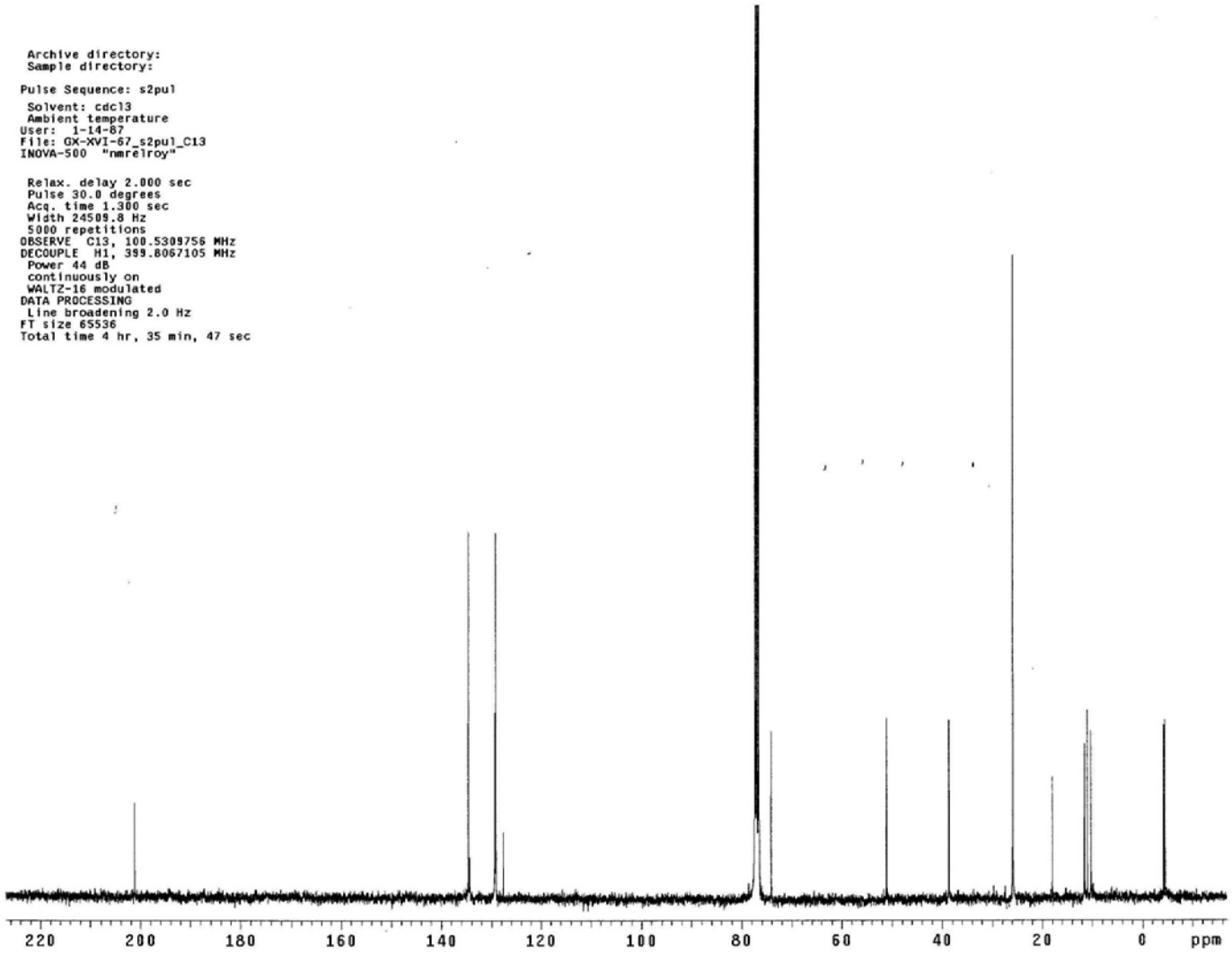
ppm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Ambient temperature
User: 1-14-87
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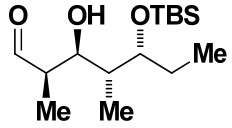
INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309756 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(*2R,3S,4R,5R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2,4-dimethylheptanal



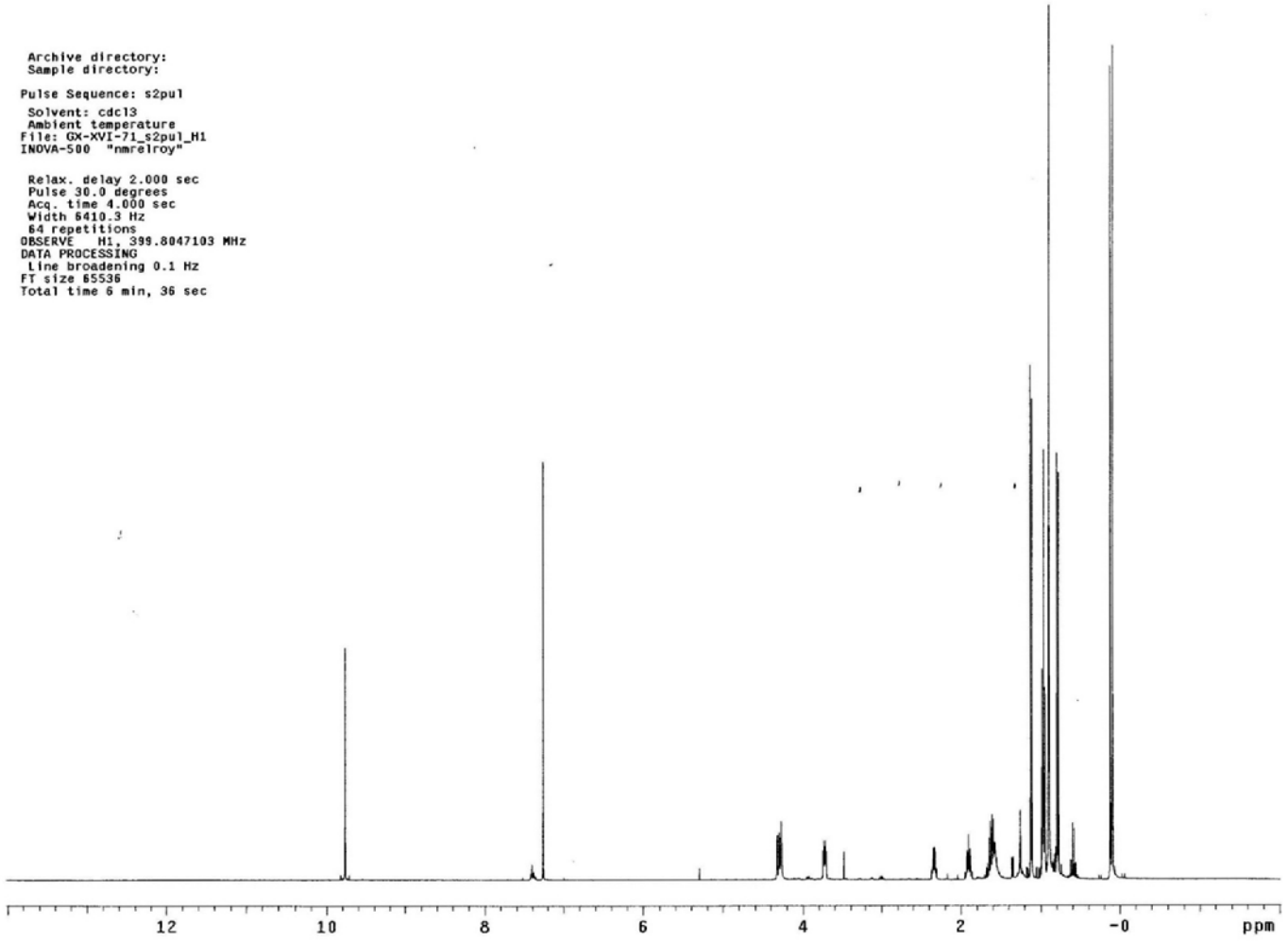
5.3a

An oven-dried round bottom flask under an atmosphere of N_2 was charged with (*2R,3S,4R,5R*)-*S*-phenyl 5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2,4-dimethylheptanethioate (230 mg, 0.58 mmol, 100 mol%), 10% Pd/C (31 mg, 0.029 mmol, 5 mol%), and acetone (11.6 mL, 0.05M). Triethylsilane (0.930 mL, 5.8 mmol, 1000 mol%) was added in ten portions and the mixture was allowed to stir at room temperature until all starting material was consumed. The reaction mixture was run through a silica plug and concentrated *in vacuo* to give the title compound (142.2 mg, 0.49 mmol) as a colorless oil in 85% yield and used in the next step without further purification.

TLC (SiO_2): R_f = 0.42 (ethyl acetate:hexanes, 1:9).

^{1}H NMR(400 MHz, $CDCl_3$): δ9.77 (d, *J* = 0.4 Hz, 1H), 4.31 (dd, *J* = 10.0, 2.4 Hz, 1H), 4.27 (s, 1H), 3.72 (dt, *J* = 8.8, 3.2 Hz, 1H), 3.34 (qd, *J* = 6.8, 2.0 Hz, 1H), 1.91 (dqd, *J* = 8.8, 7.2, 2.8 Hz, 1H), 1.68-1.52 (m, 2H), 1.12 (d, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.6 Hz, 3H), 0.90 (s, 9H), 0.79 (d, *J* = 7.2 Hz, 3H), 0.12 (s, 3H), 0.09 (s, 3H).

FTIR (neat): υ3349, 2963, 2928, 2856, 1713, 1459, 1384, 1249, 1148, 957, 931, 833, 772, 666.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Sample directory:
Pulse Sequence: s2pul
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Ambient temperature
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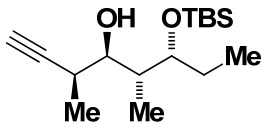
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047103 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
12
10
8
6
4
2
-0
ppm

(*3S,4R,5R,6R*)-6-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethyloct-1-yn-4-ol



5.4

An oven-dried round bottom flask under an atmosphere of N_2 was charged with Ohira-Bestmann reagent (119.9 mg, 0.62 mmol, 300 mol%) and methanol (6 mL, 0.1 M). Solid K_2CO_3 (86.2 mg, 0.62 mmol, 300 mol%) was added in one portion and the mixture was allowed to stir at room temperature for 30 min. The clear solution was transferred via syringe to another reaction flask with (*2R,3S,4R,5R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2,4-dimethylheptanal (60 mg, 0.21 mmol, 100 mol%) in THF (4.2 mL, 0.05 M) under 0 ^oC. The reaction was stirred for 1 hr and pH = 7 buffer (20 mL) was added. The layer was separated and the aqueous layer was extract with DCM (20 mL × 3). Combined organic layer was dried *in vacuo* and purified by flash column chromatography (SiO_2; hexanes:ether = 9:1) to furnish the title compound (52.7 mg, 0.19 mmol) as a colorless oil in 89% yield.

TLC (SiO_2): R_f = 0.62 (ethyl acetate:hexanes, 1:9).

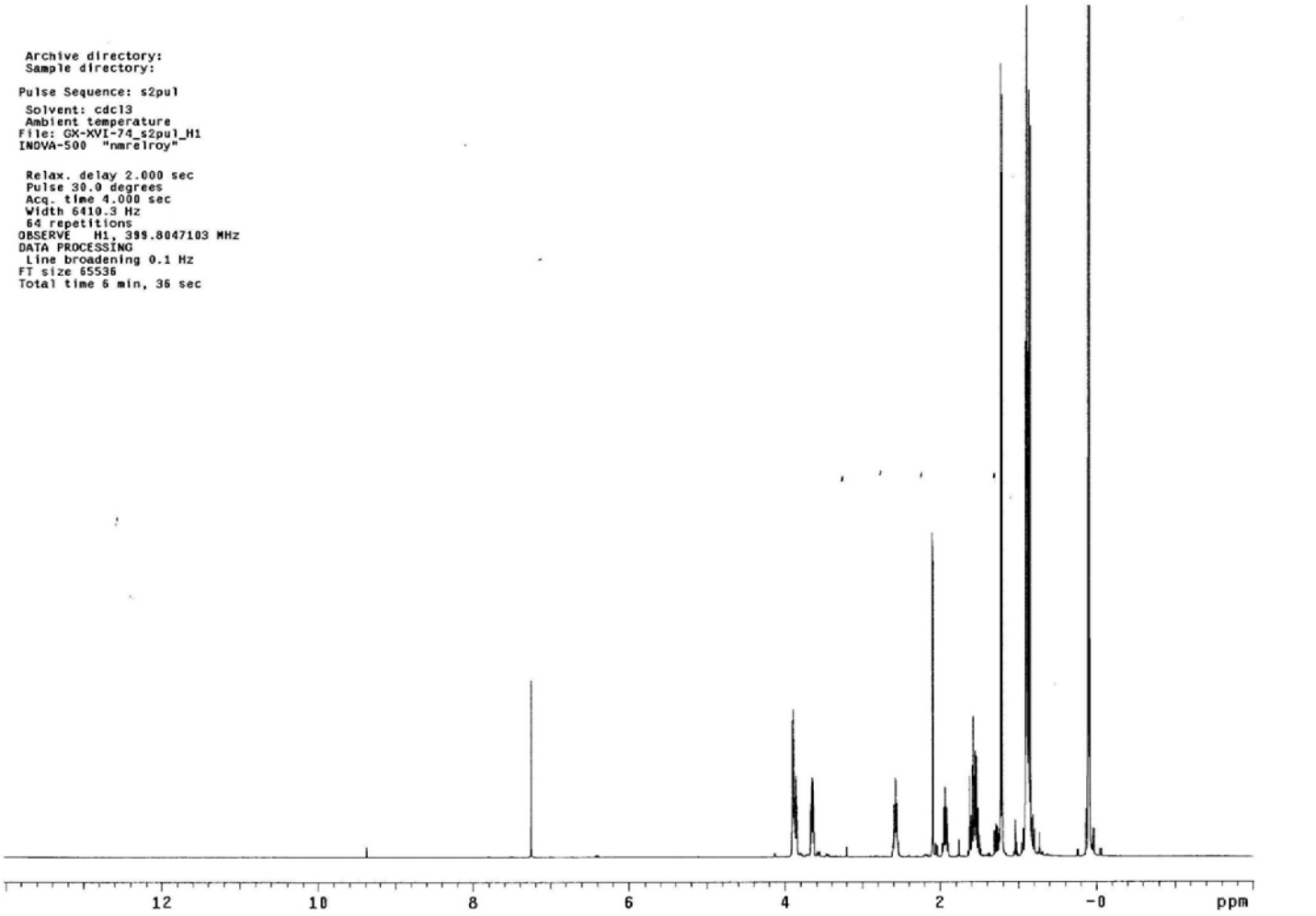
^{1}H NMR(400 MHz, $CDCl_3$): δ 3.90 (d, *J* = 4.0 Hz, 1H), 3.86 (td, *J* = 7.2, 2.0 Hz, 1H), 3.65 (p, *J* = 4.0 Hz, 1H), 2.58 (qdd, *J* = 7.2, 5.2, 2.4 Hz, 1H), 2.09 (d, *J* = 2.4 Hz, 1H), 1.93 (pd, *J* = 10.8, 2.4 Hz, 1H), 1.63-1.48 (m, 2H), 1.22 (d, *J* = 6.8 Hz, 3H), 0.89 (t, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 87.3, 77.3, 76.6, 69.2, 37.7, 29.9, 25.8, 25.6, 17.9, 14.4, 11.8, 10.8, -4.1, -4.6.

$[\alpha]_D^{25}$ = -6.1 (c = 0.33, CH_2Cl_2).

FTIR (neat): υ 2928, 2858, 1714, 1457, 1252, 1217, 1003, 954, 834, 774, 744, 688, 668.

HRMS: (CI) Calcd. for $C_{16}H_{32}O_2Si$ $[M]^+$: 284.3258, Found: 284.3253.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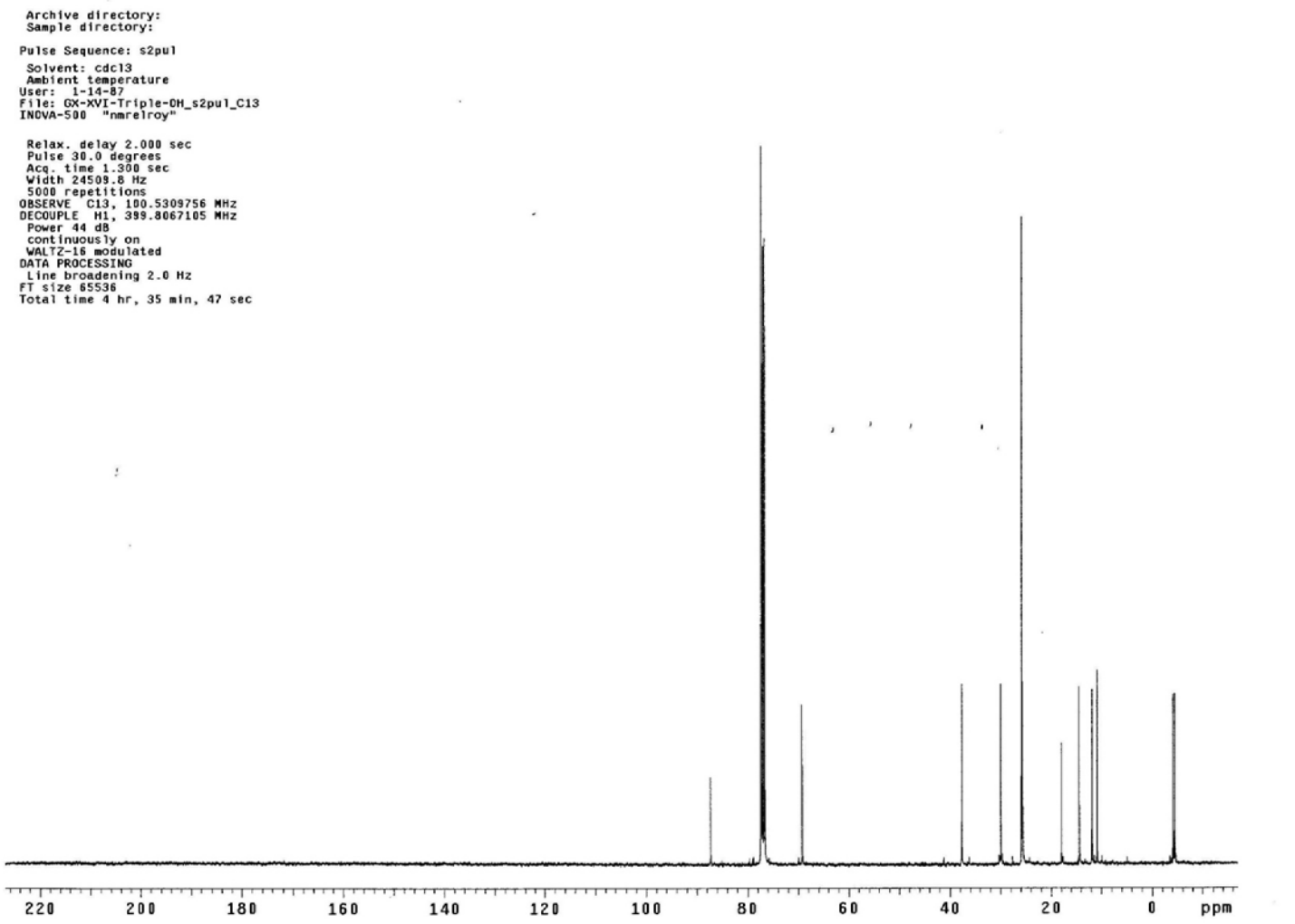
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047103 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
12
10
8
6
4
2
-0
ppm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Solvent: cdcl3
Ambient temperature
User: 1-14-87
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Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309756 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
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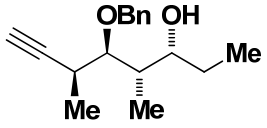
200
180
160
140
120
100
80
60
40
20
0
ppm

(*3R,4S,5R,6S*)-5-(benzyloxy)-4,6-dimethyloct-7-yn-3-ol



Fragment 5A

An oven-dried sealed tube under an atmosphere of N_2 was charged with (*3S,4R,5R,6R*)-6-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethyloct-1-yn-4-ol (350 mg, 1.23 mmol, 100 mol%), Ag_2O (855 mg, 3.69 mmol, 300 mol%) and benzyl bromide (2.104 g, 12.3 mmol, 1000 mol%). The mixture was allowed to stir at 50 ^oC for 24 hr. Methanol (5 mL) was added to the reaction mixture and the reaction was acidified by conc. HCl (~0.5 mL). After stirring for 30 min under room temperature, pH = 7 buffer (10 mL) was added and the mixture was transferred to a separatory funnel. The aqueous layer was extract with DCM (20 mL × 3). Combined organic layer was dried *in vacuo* and purified by flash column chromatography (SiO_2; hexanes:ether = 9:1) to furnish the title compound (230.6 mg, 0.886 mmol) as a colorless oil in 72% yield.

TLC (SiO_2): R_f = 0.48 (ethyl acetate:hexanes, 1:9).

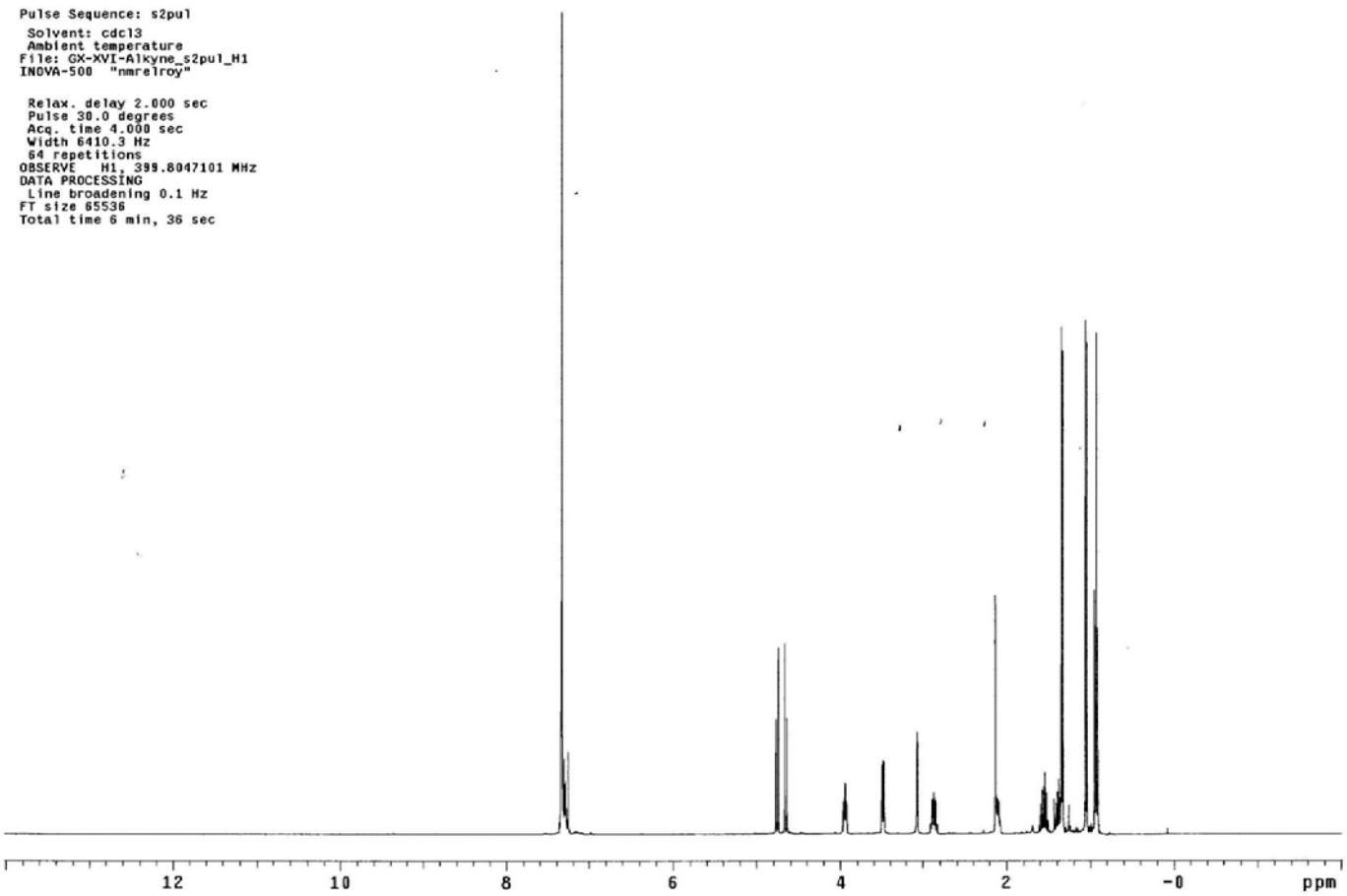
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.35-7.28 (m, 5H), 4.76 (d, *J* = 10.8 Hz, 1H), 4.65 (d, *J* = 10.8 Hz, 1H), 3.96-3.93 (m, 1H), 3.49 (dd, *J* = 8.0, 3.6 Hz, 1H), 3.07 (d, *J* = 1.6 Hz, 1H), 2.87 (dqd, *J* = 10.0, 6.8, 2.8 Hz, 1H), 2.13 (d, *J* = 2.8 Hz, 1H), 2.11 (qdd, *J* = 6.8, 4.0, 1.6 Hz, 1H), 1.62-1.51 (m, 1H), 1.43-1.32 (m, 1H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 137.6, 128.5, 128.0, 127.9, 88.2, 86.3, 76.0, 72.1, 70.5, 38.2, 29.4, 27.3, 17.3, 11.4, 10.6.

$[\alpha]_D^{25}$ = -9.3 (c = 0.22, CH_2Cl_2).

FTIR (neat): υ 3484, 3302, 2968, 2935, 2876, 1454, 1378, 1347, 1117, 1052, 953, 735, 699.

HRMS: (CI) Calcd. for $C_{17}H_{25}O_2$ $[M+H]^+$: 261.1855, Found: 261.1860.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Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047101 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
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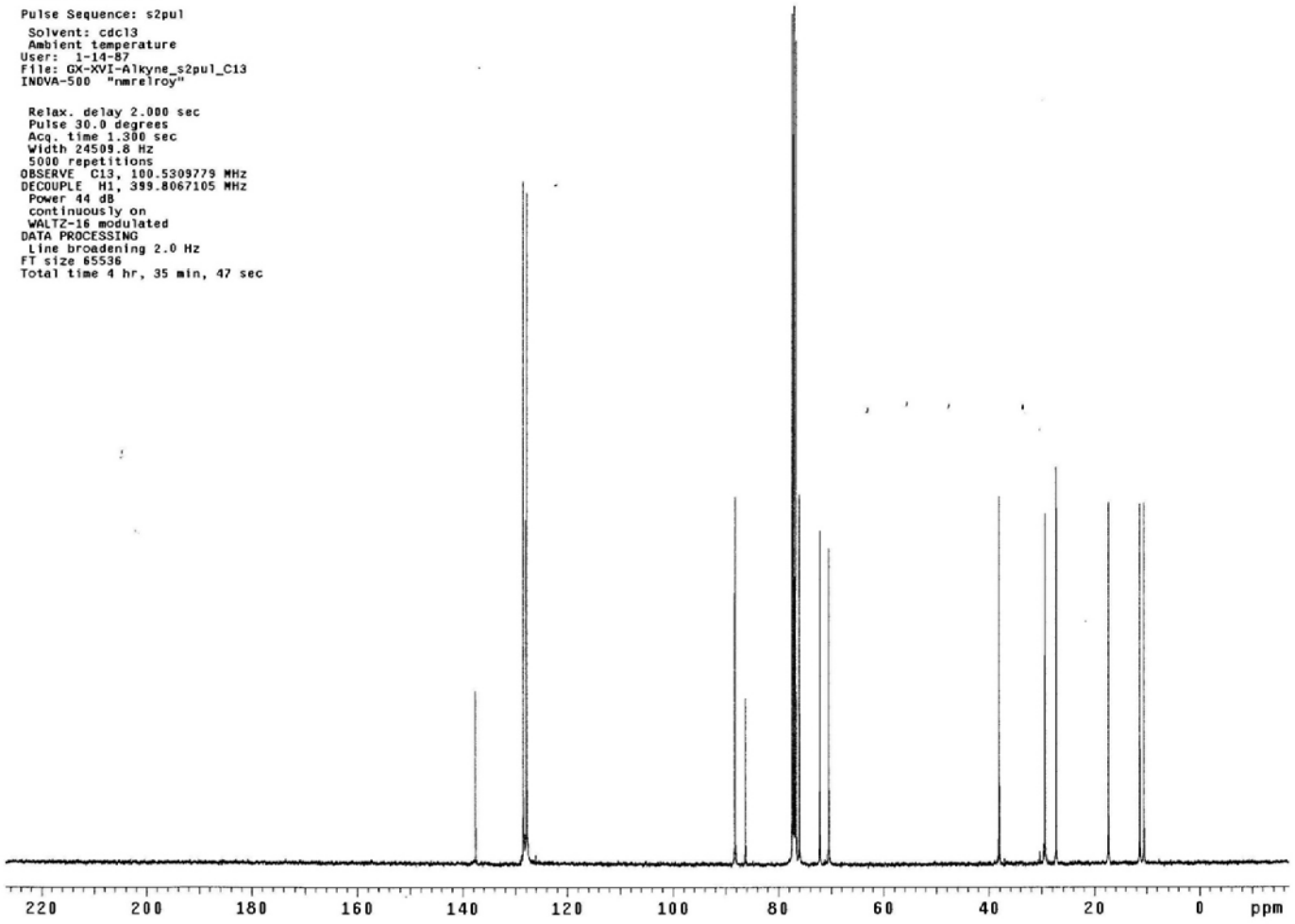
10
8
6
4
2
-0
ppm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Solvent: cdcl3
Ambient temperature
User: 1-14-87
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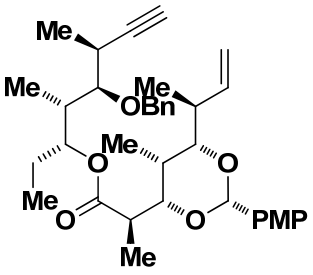
INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309779 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(*R*)-(*3R,4S,5R,6S*)-5-(benzyloxy)-4,6-dimethyloct-7-yn-3-yl 2-((*2S,4S,5R,6S*)-6-((*S*)-but-3-en-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propanoate



5.11

An oven-dried round bottom flask under an atmosphere of N_2 was charged with acid fragment (77.1 mg, 0.23 mmol, 100 mol%), triethylamine (64.3 μL, 0.46 mmol, 200 mol%) and THF (2.3 mL, 0.1 M). 2,4,6-Trichlorobenzoyl chloride (72 μL, 0.46 mmol, 200 mol%) was added and the mixture was allowed to stir at room temperature for 3 hr. The reaction mixture was filtered through a Celite plug and concentrated *in vacuo*. The residue was dissolved in toluene (1.5 mL) and added to a mixture of alcohol fragment (60.0 mg, 0.23 mmol, 100 mol%), DMAP (112.6 mg, 0.92 mmol, 400 mol%) and toluene (2.3 mL, 0.1 M). The reaction mixture was stirred at room temperature overnight, and loaded on to column directly. Purification by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20) provides the title compound (90.6 g, 0.16 mmol) as a colorless oil in 70% yield.

TLC (SiO_2): R_f = 0.59 (ethyl acetate:hexanes, 1:9).

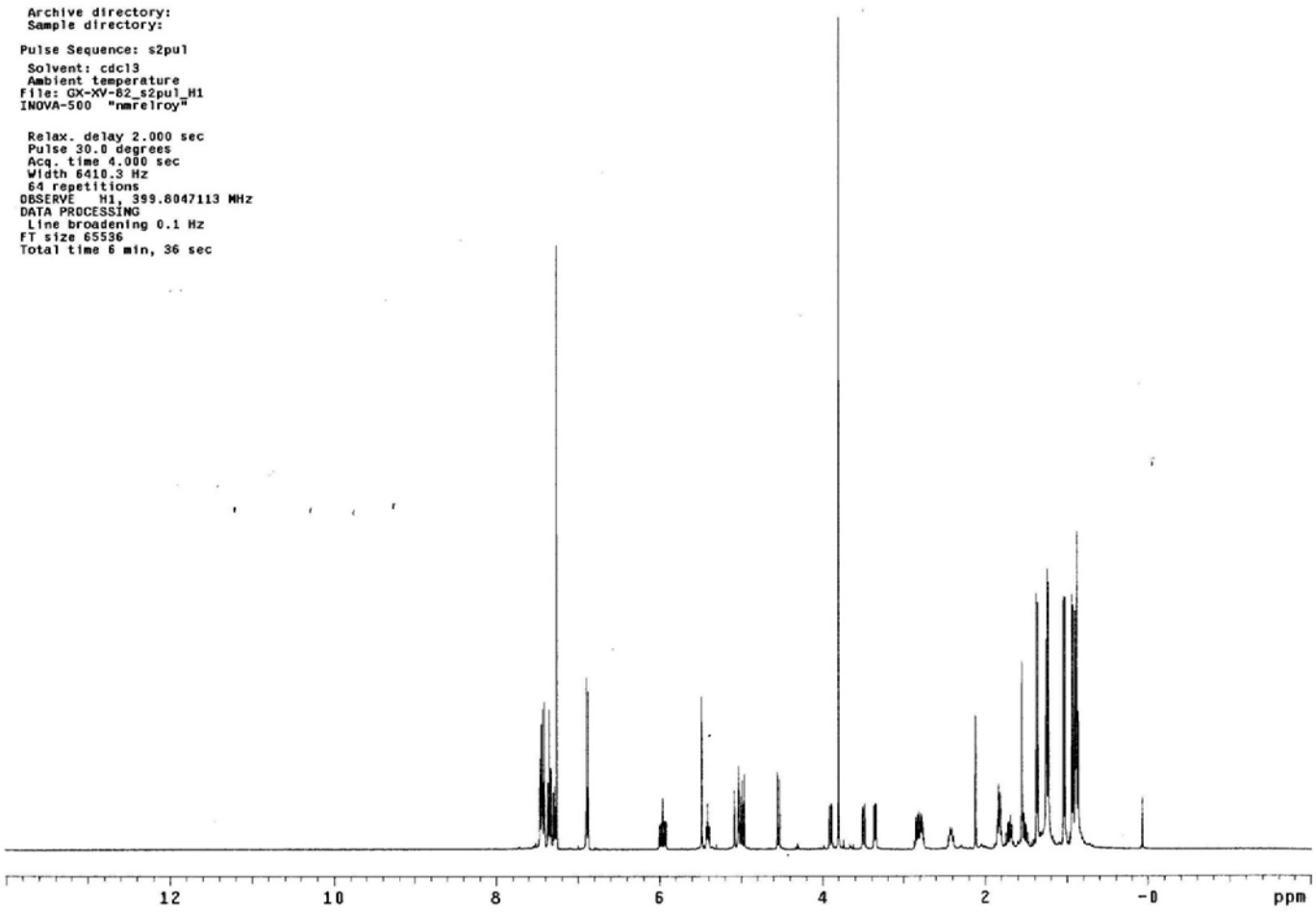
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.47-7.28 (m, 7H), 6.90-6.88 (m, 2H), 5.96 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.48 (s, 1H), 5.41 (td, *J* = 8.4, 2.4 Hz, 1H), 5.08-5.00 (m, 2H), 4.97 (d, *J* = 10.0, 1H), 4.54 (d, *J* = 10.0, 1H), 3.90 (dd, *J* = 10.4, 2.0 Hz, 1H), 3.80 (s, 3H), 3.50 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.36 (dd, *J* = 10.8, 2.8 Hz, 1H), 2.87-2.75 (m, 2H), 2.41 (qd, *J* = 6.8, 1.6 Hz, 1H), 2.11 (d, *J* = 2.4 Hz, 1H), 1.86-1.80 (m, 2H), 1.74-1.67 (m, 1H), 1.55-1.49 (m, 1H), 1.37 (d, *J* = 6.8 Hz, 3H), 1.24 (d, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.98 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 159.7, 141.6, 138.4, 131.3, 128.3, 128.3, 127.7, 127.1, 113.9, 113.5, 101.2, 87.8, 84.5, 82.2, 82.1, 74.8, 74.5, 69.8, 55.3, 42.6, 38.9, 38.1, 31.4, 27.6, 25.7, 15.7, 14.4, 14.3, 10.2, 10.2, 6.2.

$[\alpha]_D^{27}$ = -14.4 (c = 0.44, CH_2Cl_2).

FTIR (neat): υ 3090, 2970, 2972, 2940, 2924, 1740, 1454, 1377, 1350, 1121, 1052, 765, 730, 668.

HRMS: (CI) Calcd. for $C_{36}H_{47}O_6$ $[M-H]^+$: 575.3374, Found: 575.3377.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Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047113 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
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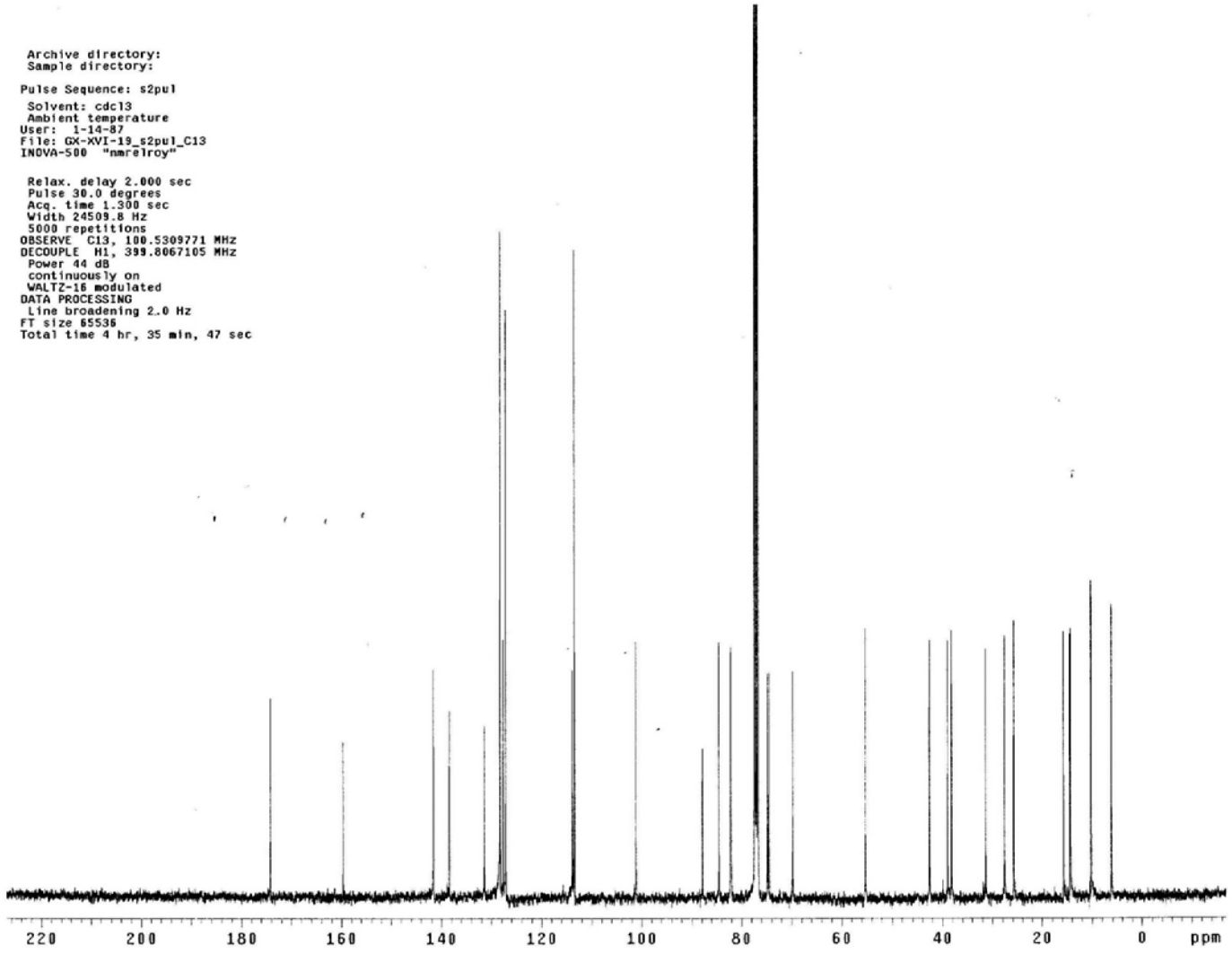
10
8
6
4
2
-0
ppm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Ambient temperature
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Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
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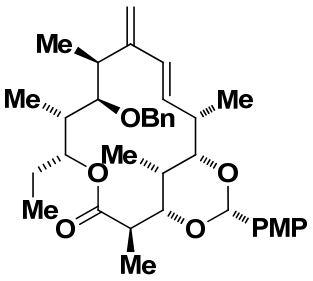
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(*1S,2R,5R,6S,7R,8S,12S,13S,15S,17R,E*)-7-(benzyloxy)-5-ethyl-15-(4-methoxyphenyl)-2,6,8,12,17-pentamethyl-9-methylene-4,14,16-trioxabicyclo[11.3.1]heptadec-10-en-3-one



5.12

An oven-dried round bottom flask under an atmosphere of ethylene (balloon pressure) was charged with (*R*)-(*3R,4S,5R,6S*)-5-(benzyloxy)-4,6-dimethyloct-7-yn-3-yl-2-((*2S,4S,5R,6S*)-6-((*S*)-but-3-en-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propanoate (105.2 mg, 0.18 mmol, 100 mol%), Hoveyda-Grubbs 2nd generation catalyst (34.3 mg, 0.60 mmol, 30 mol%) and toluene (182.4 mL, 0.001 M). The mixture was allowed to stir at 80 ^{o}C overnight. Blowing nitrogen through the reaction system to remove the ethylene and the reaction mixture was allowed to stir at 110 ^{o}C for another 24 hr followed by loading on to column directly. Purification by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20) provides the title compound (93.6 mg, 0.16 mmol) as a colorless viscous oil in 89% yield.

TLC (SiO_2): R_f = 0.62 (ethyl acetate:hexanes, 1:9).

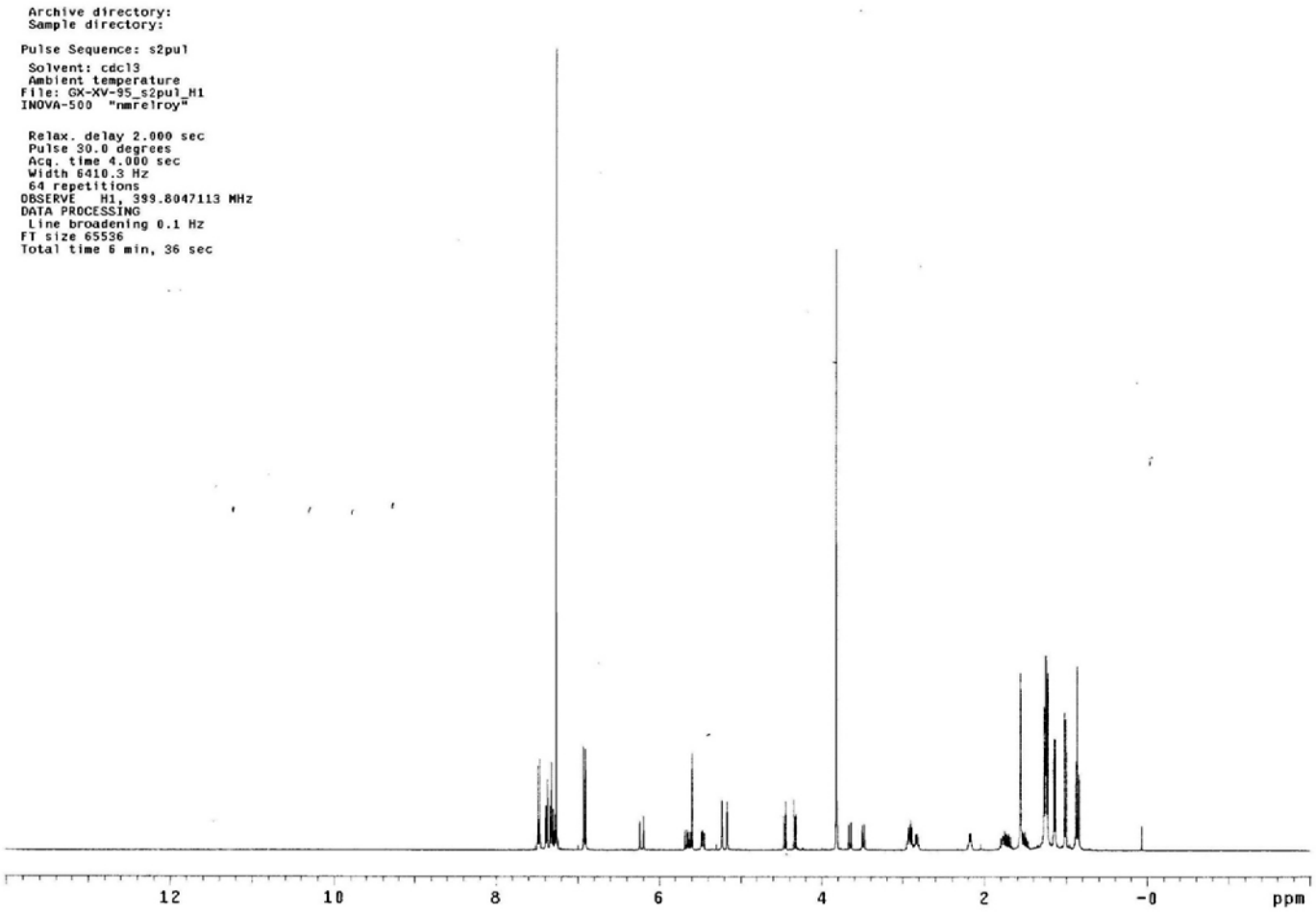
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.49-7.46 (m, 2H), 7.39-7.27 (m, 5H), 6.94-6.90 (m, 2H), 6.22 (d, *J* = 16.0 Hz, 1H), 5.65 (dd, *J* = 16.0, 9.6 Hz, 1H), 5.60 (s, 1H), 5.47 (dd, *J* = 8.4, 5.6 Hz, 1H), 5.23 (s, 1H), 5.16 (s, 1H), 4.46 (d, *J* = 9.2 Hz, 1H), 4.33 (d, *J* = 9.2 Hz, 1H), 3.83-3.80 (m, 1H), 3.82 (s, 3H), 3.65 (dd, *J* = 11.2, 1.2 Hz, 1H), 3.49 (d, *J* = 10.0 Hz, 1H), 2.96-2.80 (m, 3H), 2.17 (q, *J* = 6.8 Hz, 1H), 1.81-1.66 (m, 1H), 1.54-1.45 (m, 1H), 1.26 (d, *J* = 6.4 Hz, 3H), 1.24 (d, *J* = 6.4 Hz, 3H), 1.23 (d, *J* = 7.2 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 7.2 Hz, 3H), 0.86 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 160.0, 148.7, 138.7, 132.8, 132.7, 131.2, 128.4, 128.3, 127.6, 127.5, 115.7, 113.6, 102.6, 84.5, 83.7, 80.0, 76.0, 75.1, 55.3, 41.6, 40.2, 40.1, 35.5, 33.4, 26.5, 14.1, 13.0, 10.6, 9.9, 9.9, 9.4.

$[\alpha]_D^{27}$ = -19.9 (c = 0.58, CH_2Cl_2).

FTIR (neat): υ 2972, 2936, 2880, 1723, 1616, 1518, 1458, 1385, 1302, 1249, 1174, 1153, 1096, 1071, 1030, 1005, 891, 829, 755, 733, 699.

HRMS: (CI) Calcd. for $C_{36}H_{48}O_6$ $[M]^+$: 576.3452, Found: 576.3442.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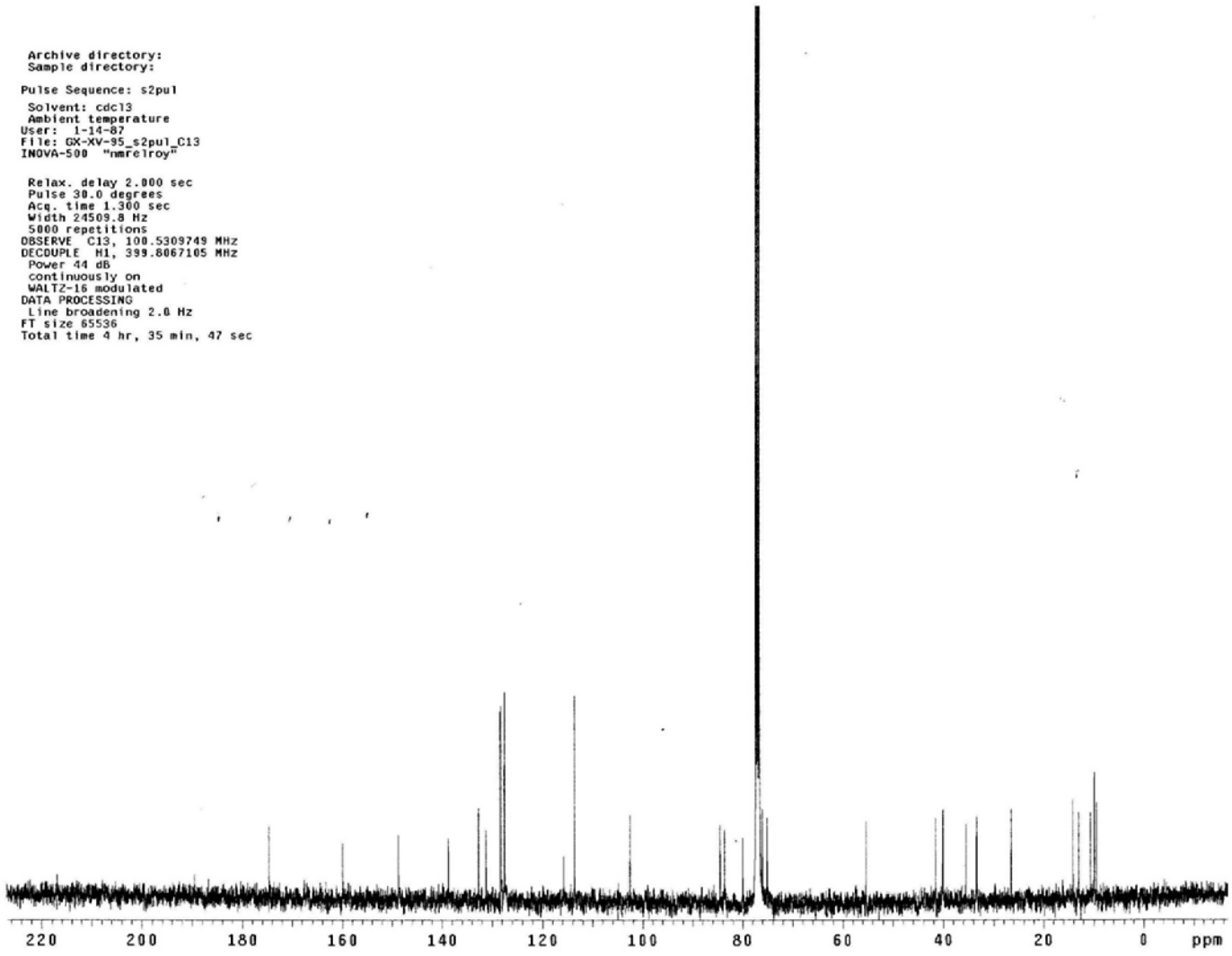
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047113 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
12
10
8
6
4
2
-0
ppm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Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
User: 1-14-87
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INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309749 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
220
200
180
160
140
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100
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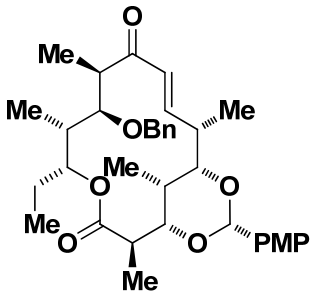
60
40
20
0
ppm

(*1S,2R,5R,6S,7S,8R,12S,13S,15S,17R,E*)-7-(benzyloxy)-5-ethyl-15-(4-methoxyphenyl)-2,6,8,12,17-pentamethyl-4,14,16-trioxabicyclo[11.3.1]heptadec-10-ene-3,9-dione



5.13

An oven-dried round bottom flask under an atmosphere of N_2 was charged with (*1S,2R,5R,6S,7R,8S,12S,13S,15S,17R,E*)-7-(benzyloxy)-5-ethyl-15-(4-methoxyphenyl)-2,6,8,12,17-pentamethyl-9-methylene-4,14,16-trioxabicyclo[11.3.1]heptadec-10-en-3-one (33.0 mg, 0.0607 mmol, 100 mol%) and THF:H_2O (3.0 mL, 1:1, 0.02 M). OsO_4 in *t*-butanol (0.303 mL, 0.02M, 0.00607 mmol, 10 mol%) was added under 0 ^oC and NMO (27.1 g, 0.200 mmol, 300 mol%) was added in one portion. The reaction mixture was stirred overnight, and solid $NaIO_4$ (66.5 mg, 0.243 mmol, 400 mol%) was added in one portion. Stirring was continued for another 12 hr fallowed by saturated aqueous $Na_2S_2O_3$ (8 mL) was added. The reaction mixture was stirred vigorously for 15 min and then transferred to a separatory funnel. The aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:20) to give the title compound (19.3 mg, 0.0334 mmol) as a colorless oil in 55% yield.

TLC (SiO_2): R_f = 0.33 (ethyl acetate:hexanes, 1:9).

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.48-7.45 (m, 2H), 7.41-7.28 (m, 5H), 6.93-6.91 (m, 2H), 6.59 (dd, *J* = 16.4, 9.6 Hz, 1H), 6.10 (dd, *J* = 16.4 Hz, 1H), 5.61 (s, 1H), 5.51 (dd, *J* = 8.8, 5.6 Hz, 1H), 4.26-4.20 (m, 2H), 3.87 (dd, *J* = 7.6, 1.2 Hz, 1H), 3.82 (s, 3H), 3.75 (d, *J* = 10.0 Hz, 1H), 3.66 (d, *J* = 10.0 Hz, 1H), 3.27 (q, *J* = 6.4 Hz, 1H), 3.08-2.99 (m, 1H), 2.95-2.87 (m, 1H), 2.07-2.02 (m, 1H), 1.85-1.68 (m, 2H), 1.63-1.45 (m, 1H), 1.30 (d, *J* =

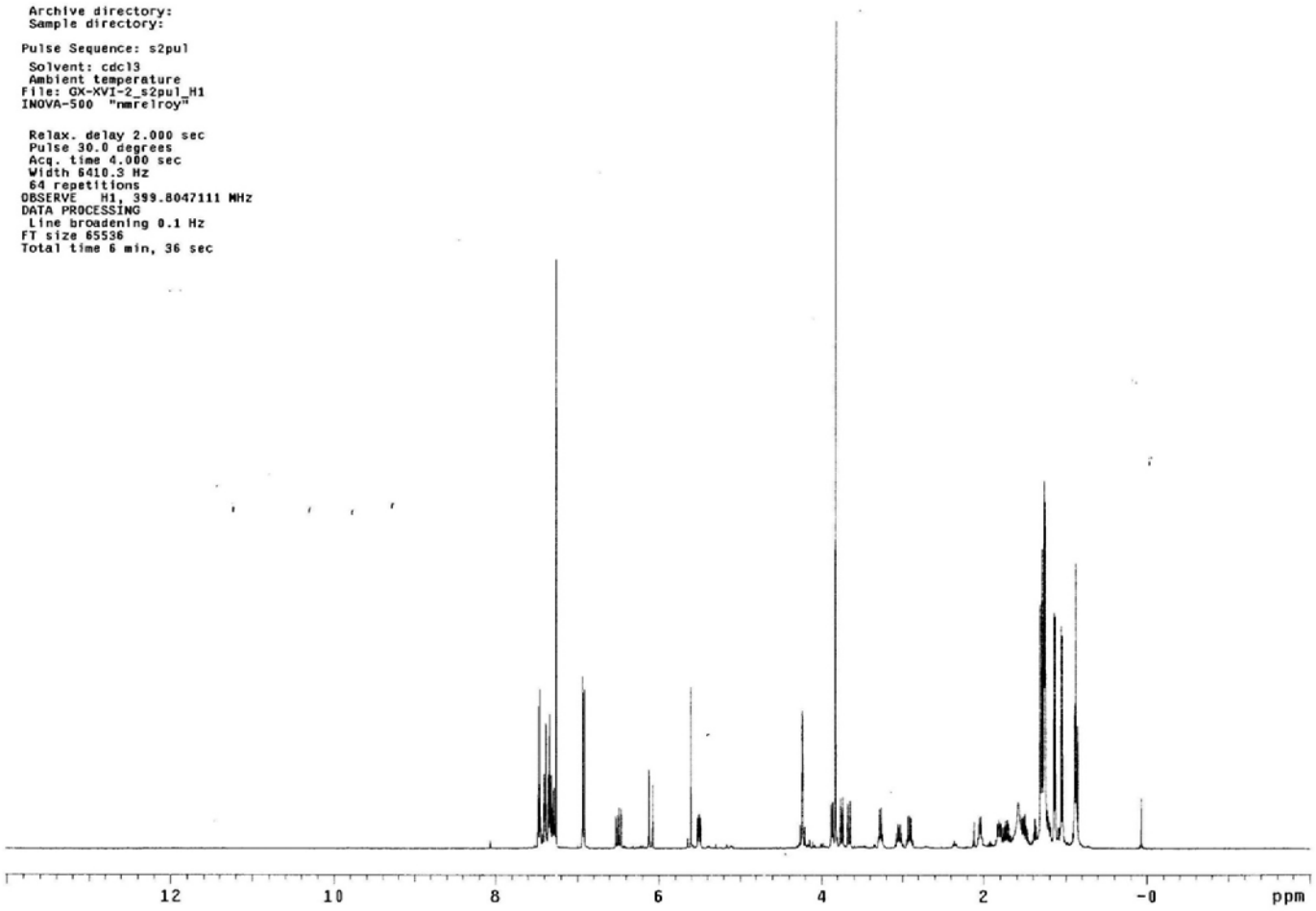
6.8 Hz, 3H), 1.28 (d, J = 7.2 Hz, 3H), 1.26 (d, J = 6.8 Hz, 3H), 1.14 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 7.2 Hz, 3H), 0.87 (t, J = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.4, 174.5, 160.0, 147.4, 137.5, 131.6, 130.8, 128.8, 128.4, 127.9, 127.5, 113.6, 102.7, 84.2, 82.4, 80.9, 75.7, 73.7, 55.3, 43.8, 41.6, 40.2, 40.0, 33.6, 26.4, 13.5, 13.1, 10.5, 10.1, 9.5, 6.7.

$[\alpha]_D^{27}$ = -33.7 (c = 0.21, CH_2Cl_2).

FTIR (neat): υ 3477, 2930, 1734, 1628, 1455, 1377, 1247, 1188, 1099, 1022, 808, 630.

HRMS: (CI) Calcd. for $C_{35}H_{47}O_7$ $[M+H]^+$: 579.3323, Found: 579.3330.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Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047111 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
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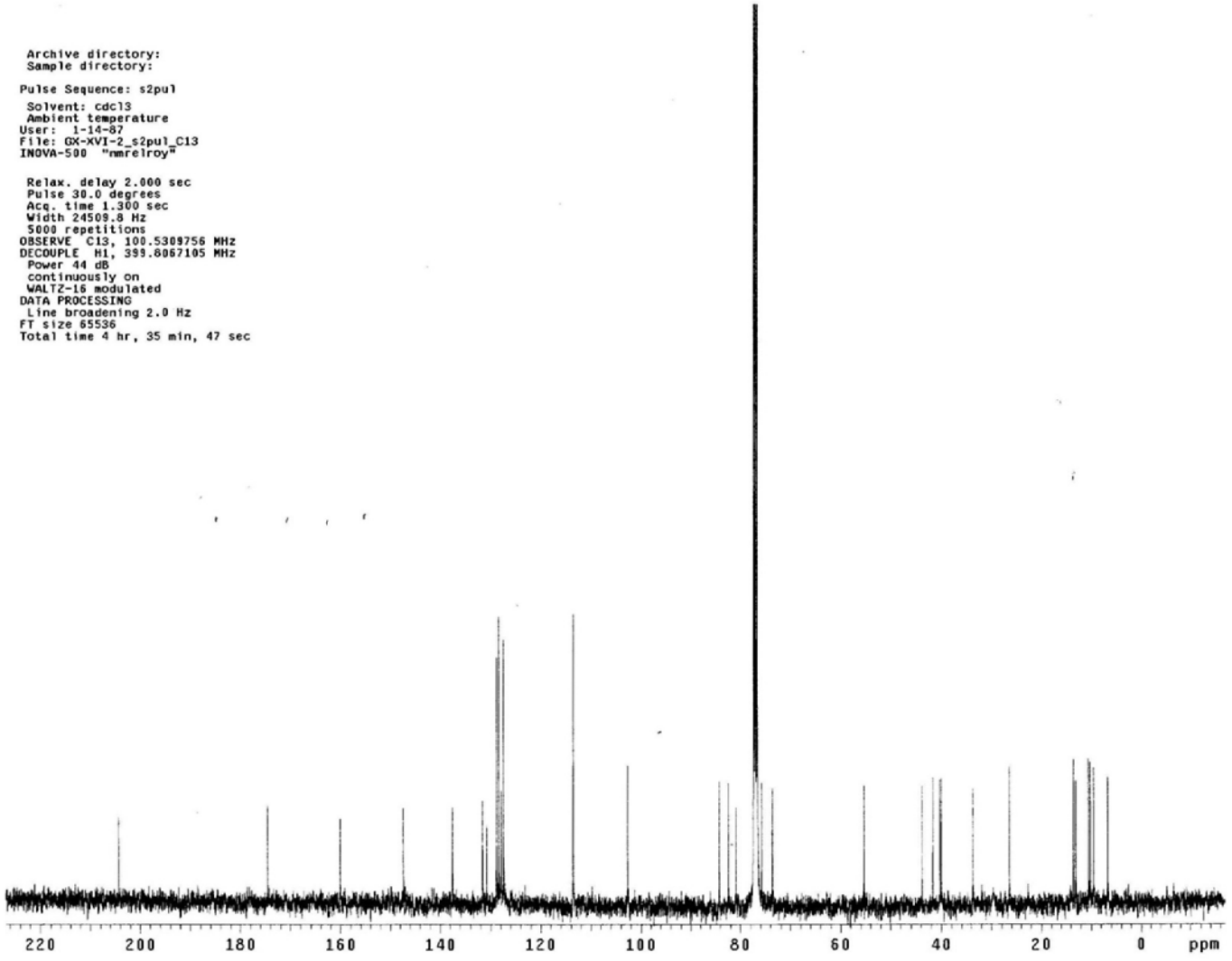
10
8
6
4
2
-0
ppm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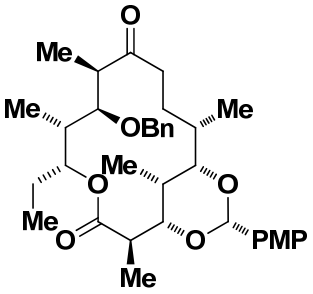
Ambient temperature
User: 1-14-87
File: GX-XVI-2_s2pul_C13
INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309756 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(*1S,2R,5R,6S,7S,8R,12S,13S,15S,17R*)-7-(benzyloxy)-5-ethyl-15-(4-methoxyphenyl)-2,6,8,12,17-pentamethyl-4,14,16-trioxabicyclo[11.3.1]heptadecane-3,9-dione



5.13a

A solution of **5.13** (12.3 mg, 0.0213 mmol, 100 mol%) in THF:MeOH (0.9 mL, 1:1, 0.025 M) was cooled to 0 °C. To this solution was added $NiCl_2$ hexahydrate (2.5 mg, 0.0106 mmol, 50 mol%) in one portion. The reaction was stirred at 0 °C for 10 min, and $NaBH_4$ (1.6 mg, 0.0425 mmol, 200 mol%) was added in three portions. The reaction mixture was stirred for another 1 hr. Purification by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20) gave the title compound (11.1 mg, 0.0191 mmol) as a colorless oil in 90% yield, > 10:1 regioselectivity.

TLC (SiO_2): R_f = 0.31 (ethyl acetate:hexanes, 1:9).

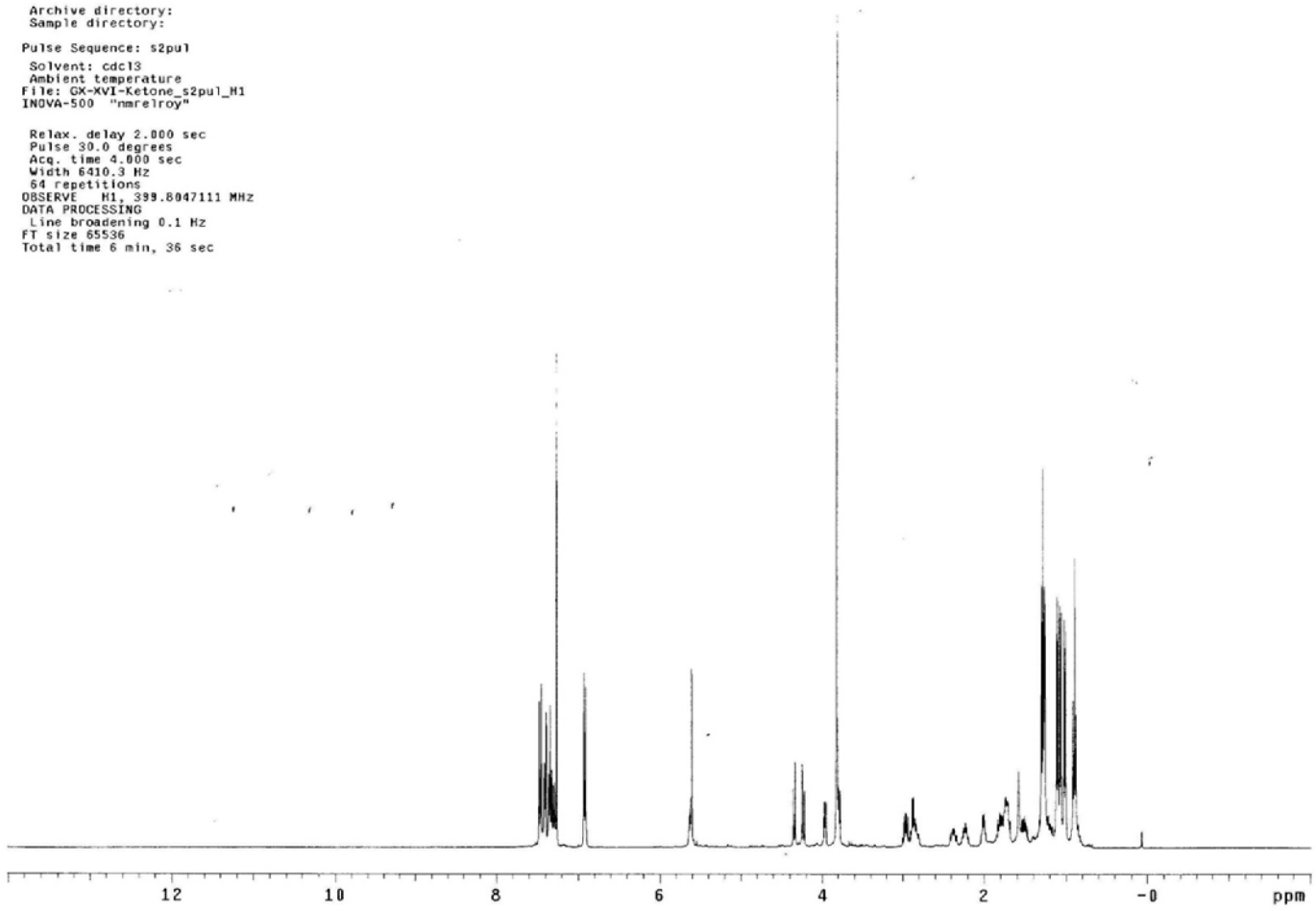
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.47-7.45 (m, 2H), 7.41-7.28 (m, 5H), 6.93-6.90 (m, 2H), 5.64-5.61 (m, 2H), 4.34 (d, *J* = 9.2 Hz, 1H), 4.23 (d, *J* = 9.2 Hz, 1H), 3.97 (d, *J* = 6.4 Hz, 1H), 3.82 (s, 3H), 3.81-3.78 (m, 2H), 3.00-2.92 (m, 1H), 2.90-2.80 (m, 2H), 2.41-2.33 (m, 1H), 2.26-2.19 (m, 1H), 2.01 (q, *J* = 6.8 Hz, 1H), 1.87-1.69 (m, 2H), 1.56-1.46 (m, 1H), 1.29 (d, *J* = 6.8 Hz, 3H), 1.27 (d, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 7.2 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 213.4, 175.2, 160.0, 137.5, 131.0, 128.6, 128.4, 127.9, 127.5, 113.6, 102.7, 84.3, 80.9, 80.2, 75.9, 72.8, 55.3, 44.9, 41.6, 40.8, 39.5, 35.0, 32.5, 30.3, 26.2, 15.8, 13.4, 10.5, 10.1, 9.2, 6.5.

$[\alpha]_D^{27}$ = -39.0 (c = 0.16, CH_2Cl_2).

FTIR (neat): υ 2972, 2940, 2923, 1730, 1717, 1366, 1214, 1099, 765, 729, 663.

HRMS: (CI) Calcd. for $C_{35}H_{48}O_7$ $[M]^+$: 580.3401, Found: 580.3400.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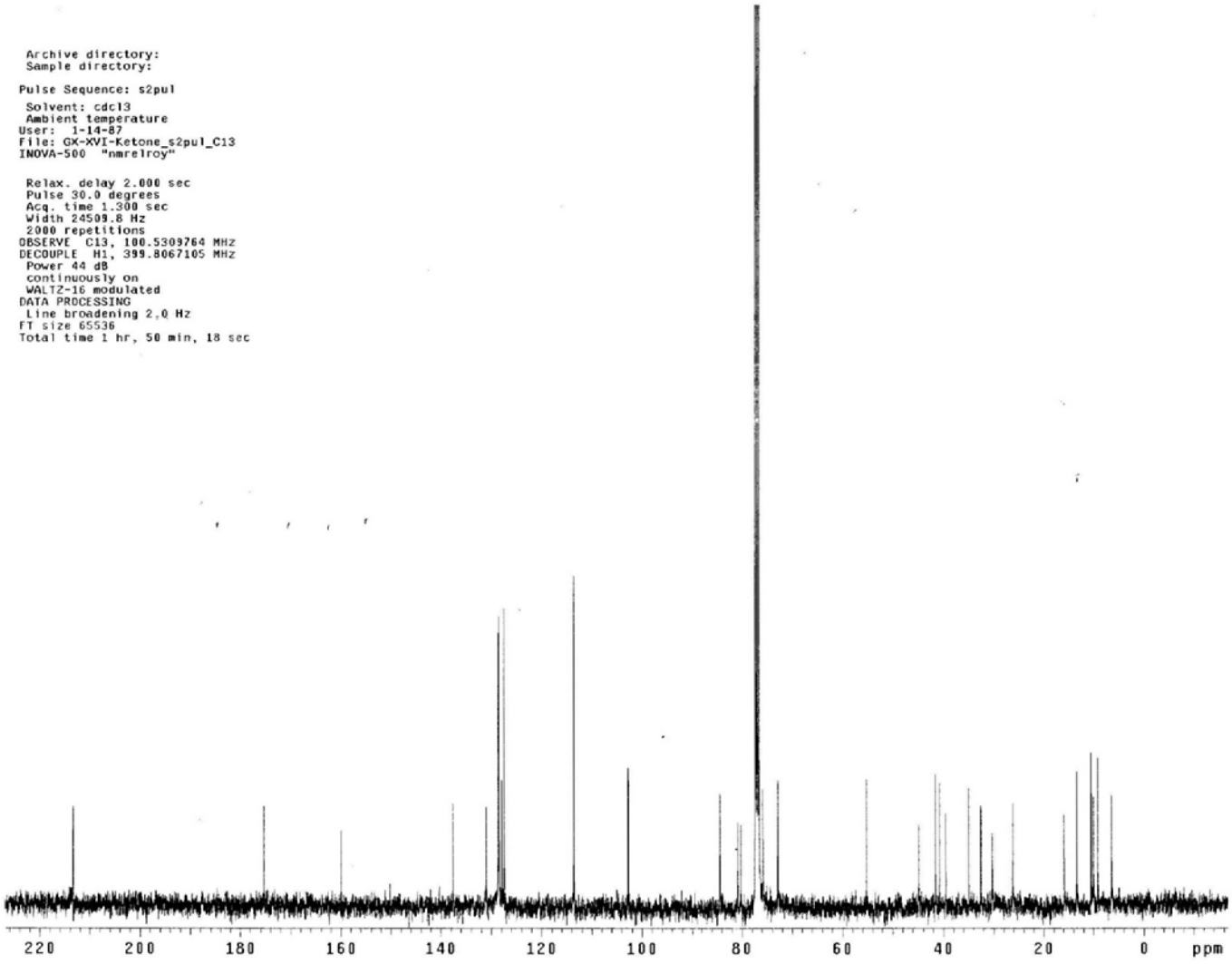
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047111 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
12
10
8
6
4
2
-0
ppm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Sample directory:
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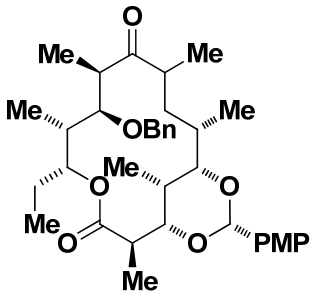
Solvent: cdcl3
Ambient temperature
User: 1-14-87
File: GX-XVI-Ketone_s2pul_C13
INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
2000 repetitions
OBSERVE C13, 100.5309764 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 1 hr, 50 min, 18 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(*1S,2R,5R,6S,7S,8R,10R,12S,13S,15S,17R*)-7-(benzyloxy)-5-ethyl-15-(4-methoxyphenyl)-2,6,8,10,12,17-hexamethyl-4,14,16-trioxabicyclo[11.3.1]heptadecane-3,9-dione



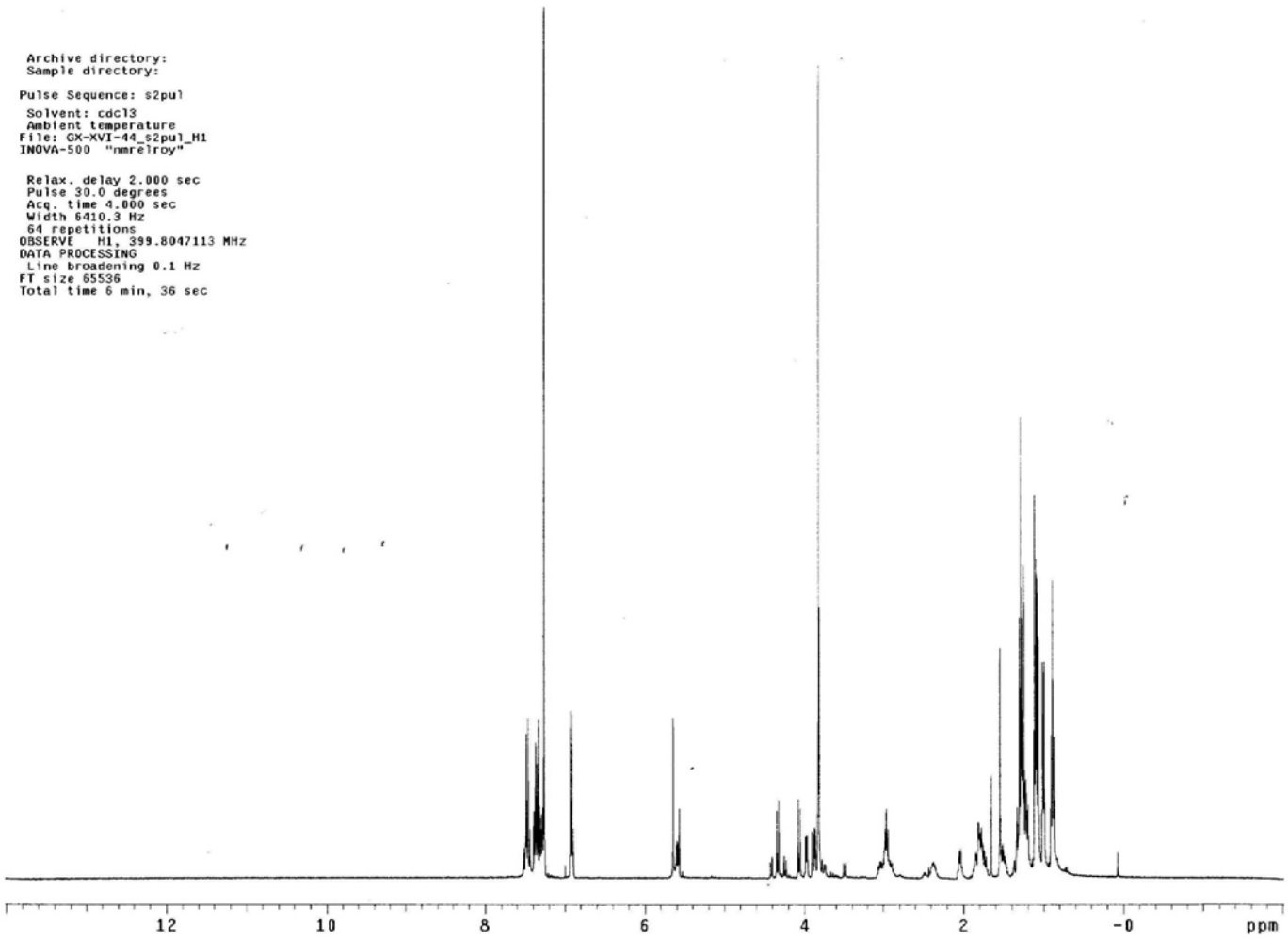
5.14

A solution of (*1S,2R,5R,6S,7S,8R,12S,13S,15S,17R*)-7-(benzyloxy)-5-ethyl-15-(4-methoxyphenyl)-2,6,8,12,17-pentamethyl-4,14,16-trioxabicyclo[11.3.1]heptadecane-3,9-dione (16.5 mg, 0.0284 mmol, 100 mol%) in THF (0.8 mL, 0.05 M) was cooled to -78 °C. To this solution was added LHMDS (0.071 mL, 1.0 M, 0.071 mmol, 250 mol%) dropwise. The reaction was stirred at -40 °C for 30 min, and recooled to -78 °C. Freshly distilled MeI (20.2 mg, 0.142 mmol, 500 mol%) was added to the reaction and the mixture was warmed to room temperature slowly. pH = 7 buffer solution was added and the mixture was extracted with ethyl ether (3 × 3 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:15) to give the title compound (14.4 mg, 0.024 mmol) as a colorless oil in 85% yield, mixture of diastereomers.

TLC (SiO_2): R_f = 0.40 (ethyl acetate:hexanes, 1:9).

FTIR (neat): υ 2971, 2934, 2034, 1701, 1618, 1518, 1454, 1305, 1248, 1173, 983, 891, 830, 809, 726, 719, 667.

HRMS: (CI) Calcd. for $C_{36}H_{51}O_7$ $[M+H]^+$: 595.3636, Found: 595.3636.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Acq. time 4.000 sec
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64 repetitions
OBSERVE H1, 399.8047113 MHz
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FT size 65536
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10
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6
4
2
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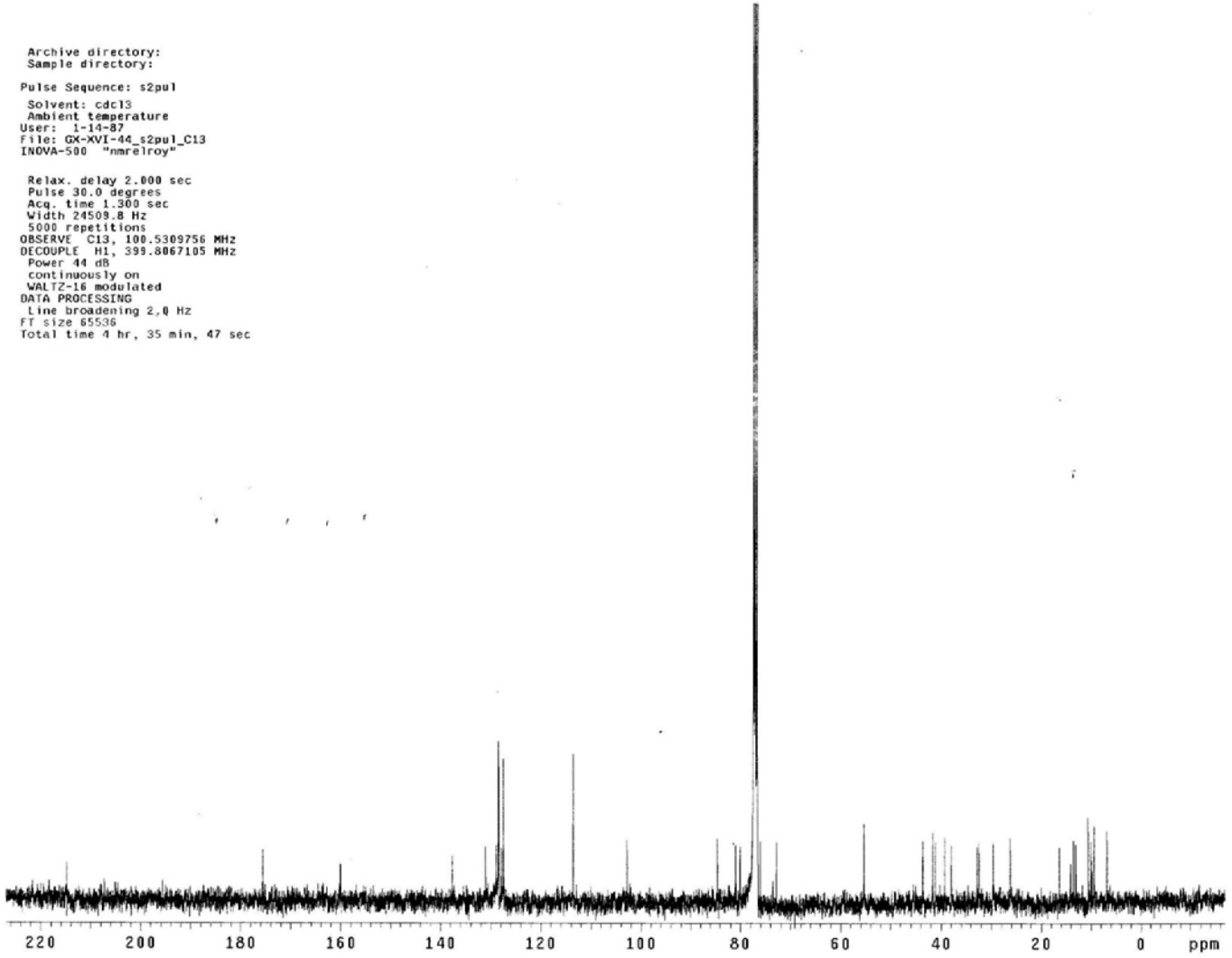
ppm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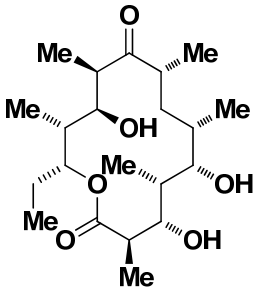
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309756 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(*3R,4S,5R,6S,7S,9R,11R,12S,13R,14R*)-14-ethyl-4,6,12-trihydroxy-3,5,7,9,11,13-hexamethyloxacyclotetradecane-2,10-dione



6-Deoxyerythronolide B

An oven-dried sealed tube under an atmosphere of H_2 was charged with (*1S,2R,5R,6S,7S,8R,10R,12S,13S,15S,17R*)-7-(benzyloxy)-5-ethyl-15-(4-methoxyphenyl)-2,6,8,10,12,17-hexamethyl-4,14,16-trioxabicyclo[11.3.1]heptadecane-3,9-dione (15 mg, 0.025 mmol, 100 mol%), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol, 40 mol%) and *i*-propanol (0.5 mL, 0.05 M). The mixture was allowed to stir at room temperature under balloon pressure of H_2 overnight. Hexane was added when reaction was finished. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:5) provides the title compound (9.0 mg, 0.0233 mmol) as a colorless viscous oil which solidified on standing in 93% yield.

TLC (SiO_2): R_f = 0.34 (ethyl acetate:hexanes, 1:3).

^{1}H NMR(500 MHz, $CDCl_3$): δ 5.15 (ddd, J = 9.5, 4.0, 1.5 Hz, 1H), 4.02-4.00 (m, 1H), 3.93 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.86 (dd, *J* = 4.5, 1.0 Hz, 1H), 3.68 (ddd, *J* = 10.5, 5.0, 2.5 Hz, 1H), 2.84 (d, *J* = 3.0 Hz, 1H), 2.82-2.74 (m, 1H), 2.66-2.50 (m, 1H), 2.08-2.00 (m, 1H), 2.01 (d, *J* = 3.5 Hz, 1H), 1.86 (qd, *J* = 6.5, 1.5 Hz, 1H), 1.84-1.79 (m, 1H), 1.74-1.72 (m, 1H), 1.70-1.65 (m, 1H), 1.55-1.50 (m, 1H), 1.30 (d, *J* = 7.0 Hz, 3H), 1.28-1.21 (m, 1H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.06 (d, *J* = 6.5 Hz, 3H), 1.05 (d, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 6.5 Hz, 1H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 213.4, 178.4, 79.5, 76.5, 76.3, 70.9, 44.0, 43.4, 40.6, 39.3, 37.7, 37.5, 35.6, 25.4, 16.6, 14.8, 13.3, 10.6, 9.2, 6.9, 6.2.

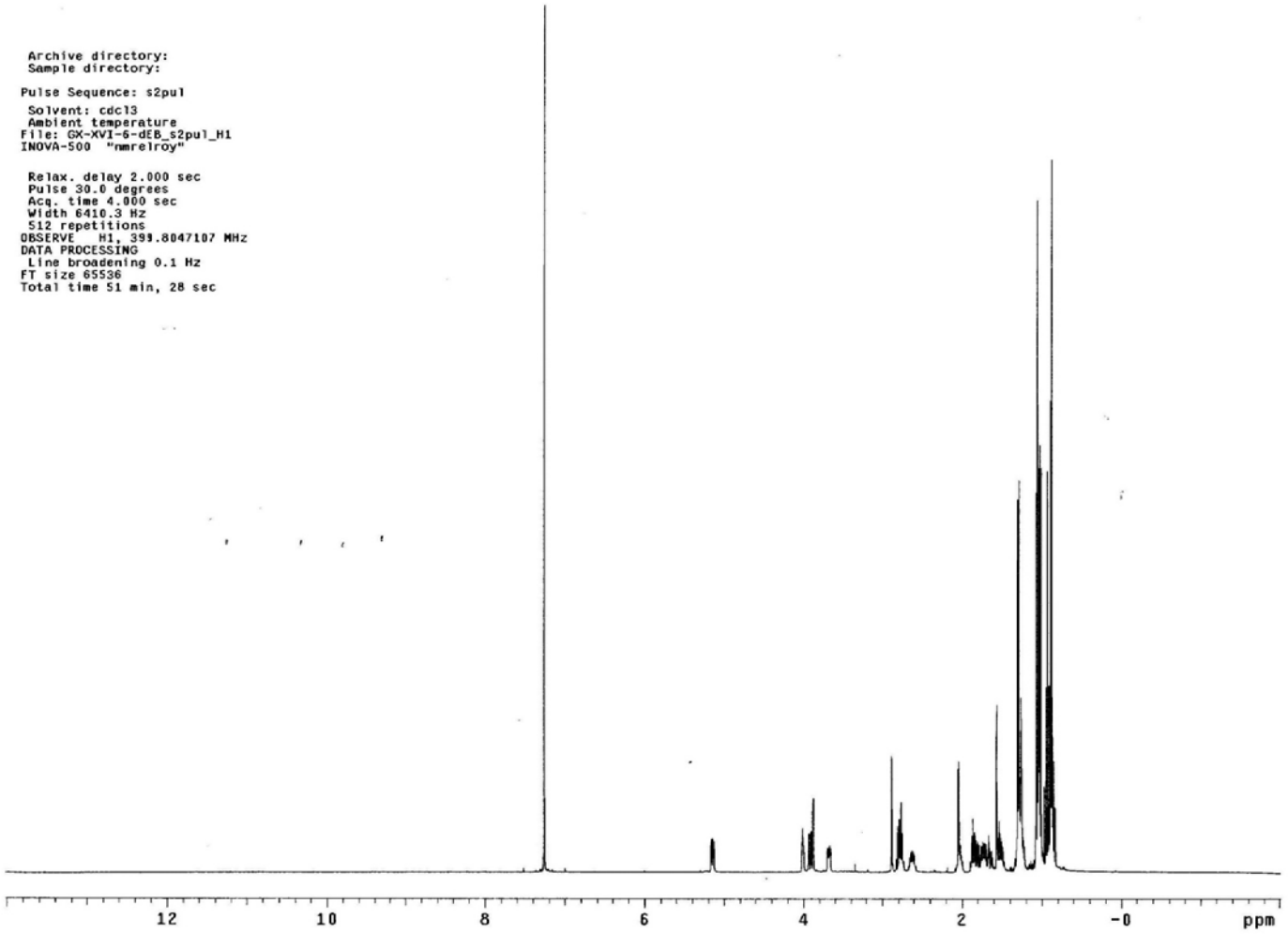
[α]$_D^{22}$ = -34.1 (c = 0.41, CH_2Cl_2).

.

FTIR (neat): υ3363, 2973, 1700, 1640, 1458, 1373, 1185, 1097, 940, 905, 727, 580.

HRMS: (CI) Calcd. for $C_{21}H_{38}O_6Na$ $[M+Na]^+$: 409.25606, Found: 409.25614.

The spectroscopic properties of this compound were consistent with the data available in the literature.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512 repetitions
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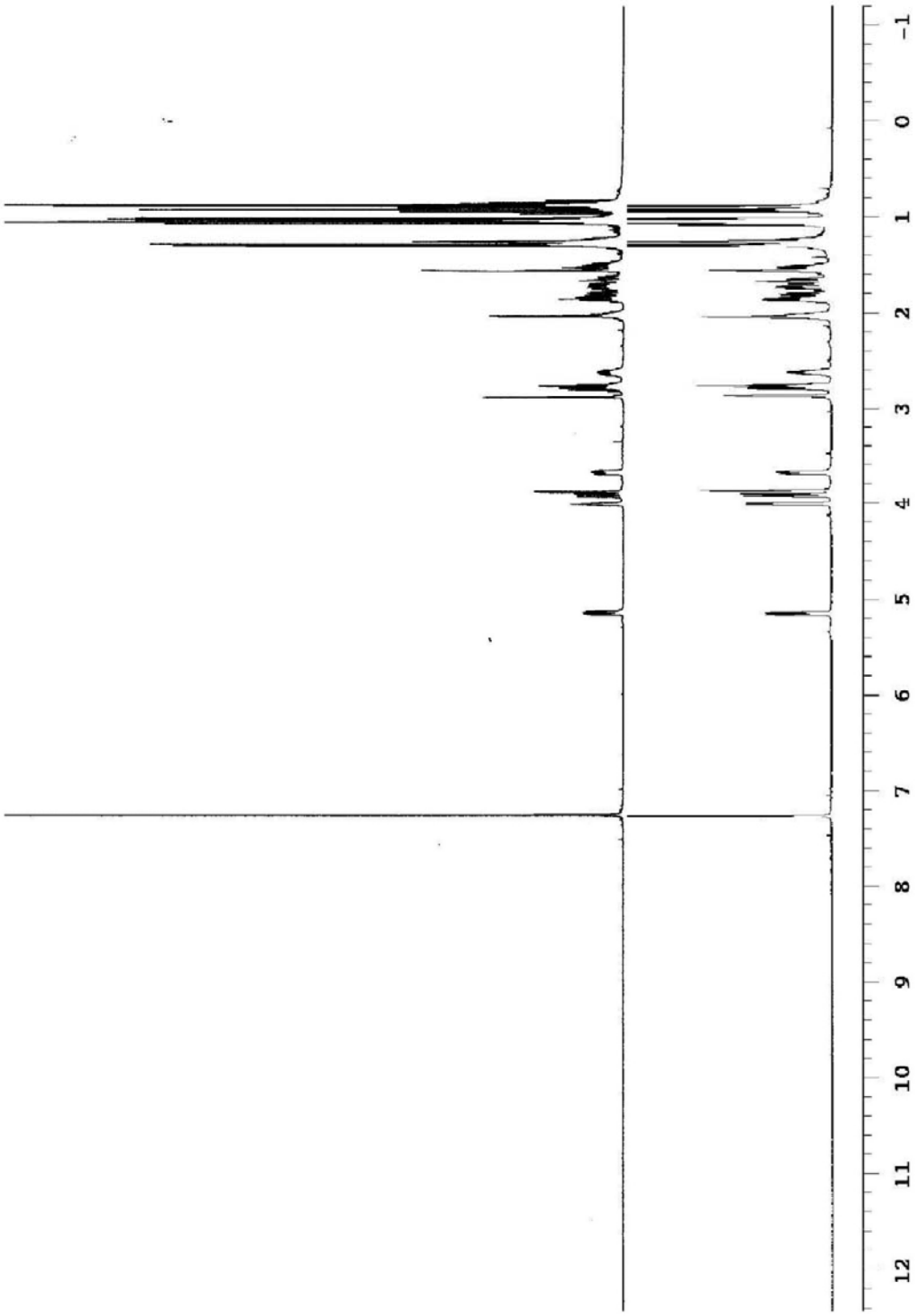
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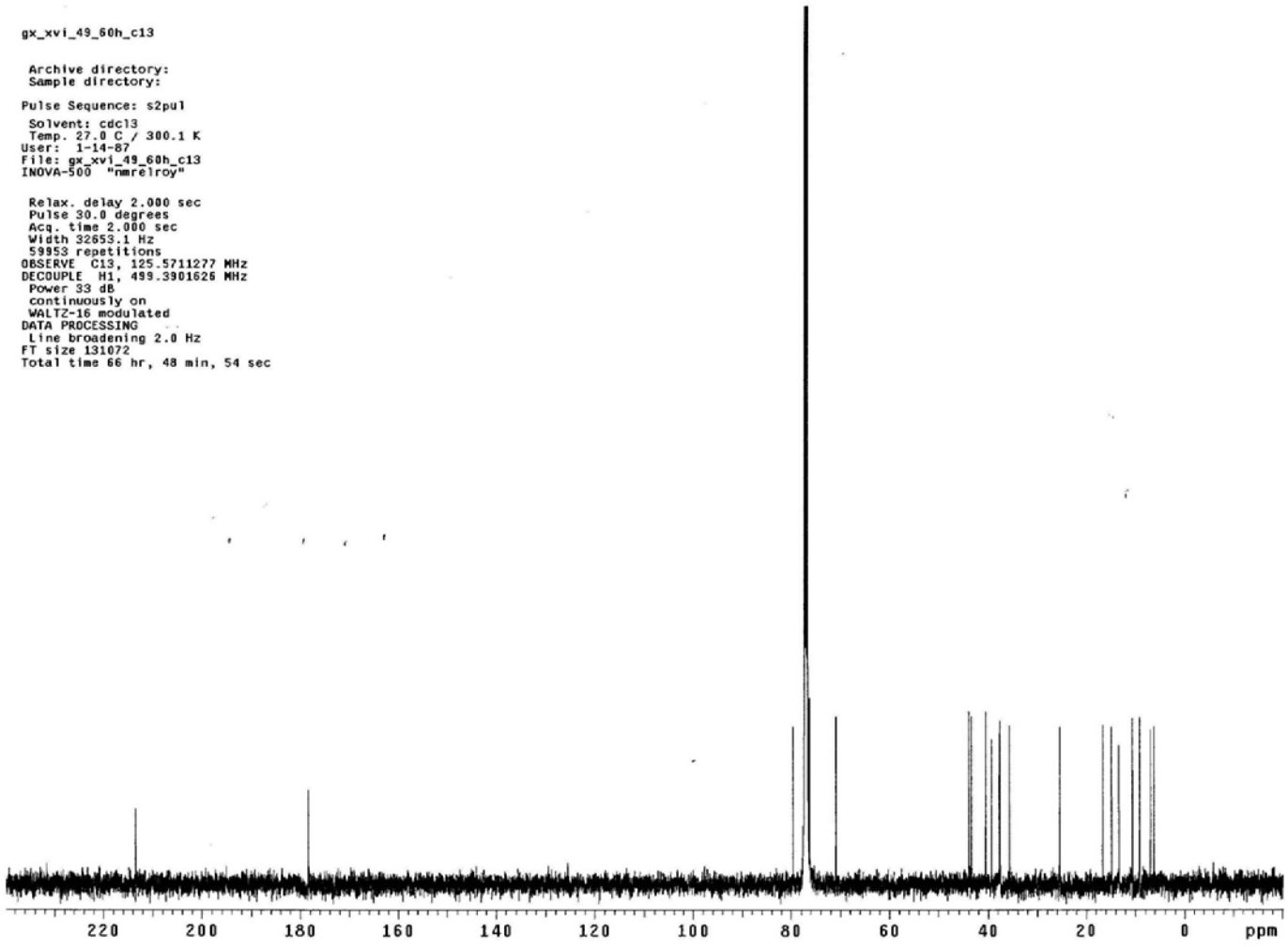
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Temp. 27.0 C / 300.1 K
User: 1-14-87
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Pulse 30.0 degrees
Acq. time 2.000 sec
Width 32653.1 Hz
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DECOUPLE H1, 499.3901626 MHz
Power 33 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 66 hr, 48 min, 54 sec
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200
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160
140
120
100
80
60
40
20
0
ppm

Target Compound Screening Report

Data File	MSF1012-0580-hrESIpos1.d	**Sample Name**	MSF1012-0580	**Comment**	GX-6-dEB
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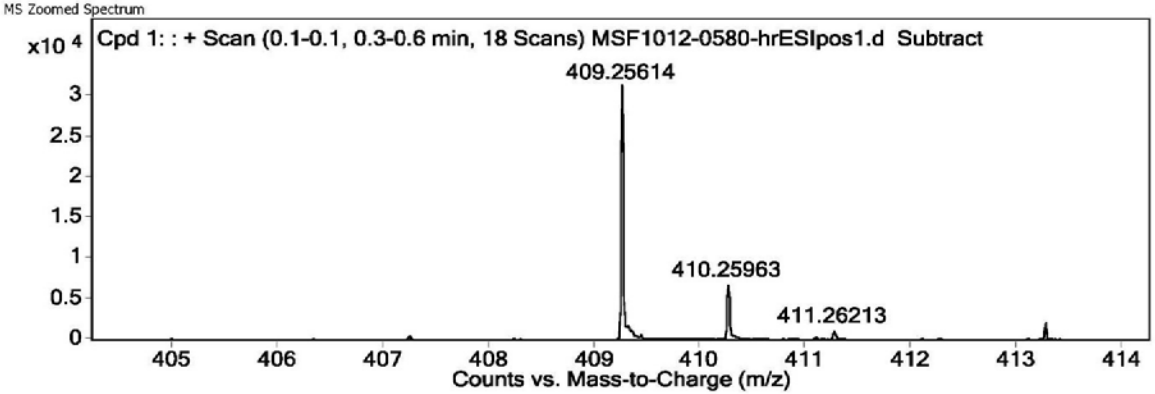
MS Zoomed Spectrum



MS Spectrum Peak List

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410.25963	410.25948	1	6974.8	C21H38NaO6	(M+Na)+	0.37
411.26213	411.26207	1	1103.3	C21H38NaO6	(M+Na)+	0.16
412.26739	412.26474	1	172.8	C21H38NaO6	(M+Na)+	6.41

--- End Of Report ---

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1	5.14 (ddd, 9.6, 4.0, 1.1)	5.15 (ddd, 9.6, 4.0, 1.0)	5.15 (ddd, 9.5, 4.0, 1.5)
2	3.99 (ddd, 4.8, 3.4, 1.7)	4.00 (m)	4.02-4.00 (m)
3	3.91 (ddd,10.3, 2.8, <1.0)	3.92 (d, 10.5)	3.93 (dd, 10.5, 3.0)
4	3.87 (d, 4.4)	3.87 (d, 4.0)	3.86 (dd, 4.5, 1.0)
5	3.67 (ddd, 10.2, 4.4, 2.0)	3.68 (ddd, 10.0, 4.5, 2.0)	3.68 (ddd, 10.5, 5.0, 2.5)
6	3.02 (d, 2.8)	2.87 (d, 1.5)	2.84 (d, 3.0)
7	2.78 (m)	2.78 (m)	2.82-2.74 (m)
8	2.62 (m)	2.63 (m)	2.66-2.50 (m)
9	2.25 (d, 3.4)	2.05-2.00 (m)	2.08-2.00 (m)
10	2.02 (m)		2.01 (d, 3.5)
11	1.86 (qd, 6.2, 1.7)	1.89-1.79 (m)	1.86 (qd, 6.5, 1.5)
12	1.82 (m)		1.84-1.79 (m)
13	1.73 (m)	1.75-1.64 (m)	1.74-1.72 (m)
14	1.67 (m)		1.70-1.65 (m)
15	1.51 (m)	1.53 (m)	1.55-1.50 (m)
16	1.29 (d, 6.7)	1.30 (d, 7.0)	1.30 (d, 7.0)
17	1.25 (m)	1.25 (m)	1.28-1.21 (m)
18	1.06 (d, 7.0)	1.07 (d, 7.0)	1.07 (d, 7.0)
19	1.04 (d, 6.4)	1.06 (d, 7.0)	1.06 (d, 6.5)
20	1.04 (d, 7.2)	1.05 (d, 7.0)	1.05 (d, 7.0)
21	1.01 (d, 6.8)	1.02 (d, 6.5)	1.02 (d, 6.5)
22	0.93 (t, 7.3)	0.93 (t, 7.5)	0.94 (t, 7.5)
21	0.88 (d, 7.0)	0.89 (d, 7.0)	0.89 (d, 7.0)

Comparison of ^{13}C NMR for Synthetic 6-Deoxyerythronolide B

Carbon#	White ($CDCl_3$, 125 MHz)	Krische ($CDCl_3$, 125 MHz)
1	213.5	213.4
2	178.4	178.4
3	79.5	79.5
4	76.5	76.5
5	76.3	76.3
6	70.9	70.9
7	43.9	44.0
8	43.4	43.4
9	40.6	40.6
10	39.2	39.3
11	37.7	37.7
12	37.5	37.5
13	35.6	35.6
14	25.4	25.4
15	16.6	16.6
16	14.8	14.8
17	13.2	13.3
18	10.6	10.6
19	9.2	9.2
20	6.9	6.9
21	6.2	6.2

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